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(54) Title: NOVEL BONE MARROW NUCLEIC ACIDS AND POLYPEPTIDES

(57) Abstract: The present invention provides novel bone marrow expressed nucleic acids, novel polypeptide sequences encoded by these nucleic acids and uses thereof.

NOVEL BONE MARROW NUCLEIC ACIDS AND POLYPEPTIDES**1. BACKGROUND OF THE INVENTION****5 1.1 TECHNICAL FIELD**

The present invention provides novel bone marrow-expressed polynucleotides and bone marrow-expressed proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for example in therapeutic, diagnostic and research methods.

10 1.2 BACKGROUND

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the
15 discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the
20 state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

The bone marrow is a well-organized tissue located within the central cavity of bone. It
25 has a complex three-dimensional structure that is richly innervated and highly vascularized. Two primary cell types make up the structure of the bone marrow. These are the stromal, and parenchymal cells. Stromal cells include reticular cells such as fibroblasts, endothelial cells, adipocytes, as well as cells of the osteochondrogenic lineage. They exert important influences on osteoclastogenesis and lymphopoiesis; and have additional effects on bone turnover.
30 Parenchymal cells are comprised of the hematopoietic cells, and are important for proliferation, maturation, and migration of cells that make up the blood.

In the adult, hematopoiesis takes place primarily in the bone marrow. Therefore, all of the cells that make up the blood, such as erythrocytes, platelets, basophils, natural killer cells, eosinophils, T- and B-lymphocytes, neutrophils, macrophages, and others, are produced in this
35 structure. Each of these cells is derived from a common, self-renewing stem cell that

proliferates, and/or differentiates depending on regulatory molecules that are produced by the stromal cells. Stromal cells are predominantly a mixture of fibroblasts, macrophage/dendritic lineage cells, epithelial cells, and endothelial cells. They influence the fate of hematopoietic cells through the secretion of soluble factors, cytokines, and the expression of membrane-anchored growth factors, and cell surface recognition molecules.

Cytokines are necessary for normal hematopoiesis in the bone marrow, and provide a means of fine-tuning bone marrow function in response to stimulation. They are not only produced by stromal cells, but can also be secreted by macrophages, and antigen-stimulated T lymphocytes for the purpose of replenishing leukocytes that may be consumed during immune and inflammatory reactions. Many cytokines that influence the differentiation and expansion of hematopoietic progenitor cells are termed colony-stimulating factors, because they were initially assayed by their ability to stimulate the formation of cell colonies in bone marrow cultures. Some of these colony-stimulating factors (CSFs) include, granulocyte-CSF, granulocyte/macrophage-CSF, monocyte-CSF, Kit-ligand, interleukin (IL)-6, FLK-2 ligand, and leukemia inhibitory factor. Each of these stimulates the growth and development of various leukocytic or erythroid colonies. Other cytokines secreted in the bone marrow include IL-9, a T cell line and mast cell progenitor-stimulating factor, IL-11, a megakaryocytopoiesis stimulator, and IL-7, a cytokine that influences the survival and expansion of immature precursors committed to the B and T cell lineages. Many other cytokines are also secreted in the bone marrow.

Cell-surface molecules that represent several adhesion molecule superfamilies including integrins, selectins, sialomucins and the immunoglobulin domain-containing proteins, are important in supporting cell-cell and cell-extracellular matrix interactions in the bone marrow. These proteins are critical to the homing of progenitor cells selectively to the marrow stroma for proliferation and differentiation. They also serve to influence the fate of the progenitor cells by directing them to differentiate into a specific lineage. For example, VLA-4 directs control of late erythroid differentiation and pro-B cell maturation.

The bone marrow is also the site of B cell development. B cells begin as lymphoid stem cells that differentiate into progenitor B-cells, or pro-B cells. Pro-B cells proliferate within the bone marrow, and fill the extravascular spaces between large sinusoids in the shaft of the bone. They next mature into precursor B cells, pre-B cells. The stromal cells of the bone marrow are crucial for both pro- and pre-B cell development because they provide a source of cytokines, and a substrate for direct interaction with the pro- and pre-B cells. Pro-B cells require interaction with VCAM-1 and stem-cell factor (SCF) on the stromal cells to induce expression of the IL-7 receptor. Secretion of IL-7 by the stromal cells then induces the pro-B cells to mature into pre-B

cells. Continued IL-7 secretion by stromal cells induces pre-B cells to begin proliferating and eventually differentiates them into immature B-cells. In addition, a selection process within the bone marrow eliminates B cells with self-reactive phenotypes, functioning to protect against autoimmune disease.

5 The bone marrow environment also influences bone turnover and bone precursor cell functions. Bone marrow stromal cells include the precursors of the osteochondrogenic lineage, and can modulate the effects of some systemic factors on bone turnover. Furthermore, hematopoietic cells may influence the differentiation of osteogenic cells, and mature lymphocytes may impact osteoclastic and osteoblastic functions. For instance, B-lymphocytes
10 have been implicated in the secretion of factors that change the immunological milieu at sites of new bone induction and influence new bone formation.

 The identified bone marrow-expressed polynucleotide and polypeptide sequences may have applications in hematopoiesis, stem cell survival, and bone growth and remodeling. Identification of secreted factors that stimulate hematopoiesis may serve to produce greater
15 immune responses in immunosuppressed individuals. The identification of factors that preferentially stimulate specific hematopoietic cell types may also allow the prevention of specific disorders such as anemia in the case erythroid cell stimulating factors, or platelet deficiency in the case of megakaryocyte stimulating factors. Likewise, stem cell stimulating factors may be used to restore blood cell populations following chemotherapy treatments for
20 cancer. Therapy to stimulate bone healing and remodeling may also be identified by the discovery of novel factors in the bone marrow that influence bone resorption by osteoclasts, or new bone cell differentiation from stromal cells.

2. SUMMARY OF THE INVENTION

25 The compositions of the present invention include novel isolated polypeptides from bone marrow tissue, and novel isolated polynucleotides from bone marrow tissue encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as
30 well as hybridomas producing such antibodies.

 The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

 The present invention relates to a collection or library of at least one novel nucleic acid
35 sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by

hybridization (SBH), and in some cases, sequences obtained from one or more public databases.

The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1-84, or 168-251 are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenine; C is cytosine; G is guanosine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, * corresponds to the stop codon.

The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1-84, or 168-251 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1-84, or 168-251. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1-84, or 168-251 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO: 1-84, or 168-251. The sequence information can be a segment of any one of SEQ ID NO: 1-84, or 168-251 that uniquely identifies or represents the sequence information of SEQ ID NO: 1-84, or 168-251.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information are provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-84, or 168-251, or novel segments or parts of the nucleic acids of the invention are used as primers in expression

assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO: 1-84, or 168-251 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying bone marrow tissues and cells; for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in SEQ ID NO: 1-84, or 168-251; a polynucleotide comprising any of the full length protein coding sequences of SEQ ID NO: 1-84, or 168-251; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of SEQ ID NO: 1-84, or 168-251. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in SEQ ID NO: 1-84, or 168-251; (b) a nucleotide sequence encoding any one of the amino acid sequences comprising SEQ ID NO: 85-167, or 252-335; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in the Sequence Listing; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in SEQ ID NO: 1-84, or 168-251; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions, or (c) polypeptides comprising any of the polypeptide sequences set forth in SEQ ID NO: 85-167, or 252-335. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention. The polypeptides may have the initial methionine (Met) removed.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, *e.g.*, *in situ* hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies, are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.

The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the

identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that modulate (i.e., increase or decrease) the expression or activity of the polynucleotides and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (e.g., bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and detecting the complex by detecting the reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provide methods for treatment that involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products. Compounds and other substances can affect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have homology (set forth in Tables 1A-D); for which they have a signature region (as set forth in Table 2); or for which they have homology to a gene family (as set forth in Tables 3). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in increasing hematopoiesis, stem cell survival, and bone growth and remodeling.

3. DETAILED DESCRIPTION OF THE INVENTION

3.1 DEFINITIONS

It must be noted that as used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise.

The term “active” refers to those forms of the polypeptide that retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms “biologically active” or “biological activity” refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise “immunologically active” or “immunological activity” refers to the capability of the natural, recombinant or synthetic polypeptide to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term “activated cells” as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

The terms “complementary” or “complementarity” refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be “partial” such that only some of the nucleic acids bind or it may be “complete” such that total complementarity exists between the single stranded molecules. The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term “embryonic stem cells (ES)” refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term “germ line stem cells (GSCs)” refers to stem cells derived from primordial stem cells that provide a steady and continuous source of germ cells for the production of gametes. The term “primordial germ cells (PGCs)” refers to a small population of cells set aside from other cell lineages particularly

from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ cells and other cells. PGCs are the source from which GSCs and ES cells are derived. The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that
5 comprise the adult specialized organs, but are able to regenerate themselves.

The term "expression modulating fragment," EMF, means a series of nucleotides that modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs
10 include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs is nucleic acid fragments that induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonucleotide" are used interchangeably and refer to a heteropolymer of nucleotides or the
15 sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. It is contemplated that where the polynucleotide is RNA, the T (thymine) in the sequences provided herein is substituted with U (uracil). Generally, nucleic acid segments provided by this invention
20 may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or
25 "segment" or "probe" or "primer" are used interchangeably and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 9 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less than about 200 nucleotides, more preferably less than about 100
30 nucleotides, more preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30 nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray
35 procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A

fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NO: 1-84, or 168-251.

Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO: 1-84, or 168-251. The sequence information can be a segment of any one of SEQ ID NO: 1-84, or 168-251 that uniquely identifies or represents the sequence information of that sequence of SEQ ID NO: 1-84, or 168-251. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because 4^{20} possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosome. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these segments are used in arrays for expression studies, fifteen-mer segments can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match ($1/4^{25}$) times the increased probability for mismatch at each nucleotide position (3×25). The probability that an eighteen mer with a single mismatch can be detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent cell is restricted in its differentiation capability in comparison to a totipotent cell.

The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably at least about 7 amino acids, more preferably at least about 9 amino acids and most preferably at least about 17 or more amino acids. The peptide preferably is not greater than about 200 amino acids, more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence that encodes for the full-length protein which may include any leader sequence or any processing sequence.

The term "mature protein coding sequence" means a sequence that encodes a peptide or protein without a signal or leader sequence. The "mature protein portion" means that portion of the protein which does not include a signal or leader sequence. The peptide may have been produced by processing in the cell that removes any leader/signal sequence. The mature protein portion may or may not include an initial methionine residue. The methionine residue may be removed from the protein during processing in the cell. The peptide may be produced synthetically or the protein may have been produced using a polynucleotide only encoding for the mature protein coding sequence.

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or

substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

The term "variant"(or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, *e.g.*, recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes that produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations can, for example, alter one or more of the biological functions or biochemical characteristics of the polypeptides of the invention. For example, such alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover

rate. Further, such alterations can be selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

5 The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, *e.g.*, polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, 10 buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 Daltons, can be present).

 The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (*e.g.*, nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in 15 the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

 The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (*e.g.*, microbial, insect, or mammalian) 20 expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (*e.g.*, yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, *e.g.*, *E. coli*, will be free of glycosylation modifications; polypeptides or 25 proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

 The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements 30 having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant 35 protein is expressed without a leader or transport sequence, it may include an amino terminal

methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

The term "recombinant expression system" means host cells that have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells that have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted" proteins are also intended to include proteins containing non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g. Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M NaHPO₄, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65 °C, and washing in 0.1X SSC/0.1% SDS at 68 °C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42 °C). Other exemplary hybridization conditions are described herein in the examples.

In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37 °C (for

14-base oligonucleotides), 48 °C (for 17-base oligos), 55 °C (for 20-base oligonucleotides), and 60 °C (for 23-base oligonucleotides).

As used herein, "substantially equivalent" or "substantially similar" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (*i.e.*, the number of individual residue substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, *e.g.*, mutant, sequence of the invention varies from a listed sequence by no more than 30% (70% sequence identity); in a variation of this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no more than 20% (80% sequence identity) and in a further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more than 5% (95% sequence identity). Substantially equivalent, *e.g.*, mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 85% sequence identity, more preferably at least 90% sequence identity, more preferably at least 95% sequence identity, more preferably at least 98% sequence identity, and most preferably at least 99% sequence identity. Substantially equivalent nucleotide sequence of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code. Preferably, the nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, more preferably at least about 80% sequence identity, more preferably at least 85% sequence identity, more preferably at least 90% sequence identity, more preferably at least about 95% sequence identity, more preferably at least 98% sequence identity, and most preferably at least 99% sequence identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (*e.g.*, via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, *e.g.*, using the Jotun Hein method (Hein, J. (1990) *Methods Enzymol.* 183:626-645). Identity between sequences can also be determined by other methods known in the art, *e.g.* by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The
5 term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides that mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified
10 using known UMFs as a target sequence or target motif with the computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic acid molecule is then incubated with an appropriate host under appropriate conditions and the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked
15 marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

3.2 NUCLEIC ACIDS OF THE INVENTION

Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of SEQ ID NO: 1-84, or 168-251; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO: 85-167, or 252-335; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polynucleotides of any one of SEQ ID NO: 1-84, or 168-251. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of SEQ ID NO: 1-84, or 168-251; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO: 85-167, or 252-335. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptor-like polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of SEQ ID NO: 1-84, or 168-251 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of SEQ ID NO: 1-84, or 168-251 or a portion thereof as a probe. Alternatively, the polynucleotides of SEQ ID NO: 1-84, or 168-251 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public databases, such as dbEST, gbpr, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited above. Polynucleotides according to the invention can have, *e.g.*, at least about 65%, at least about 70%, at least about 75%, at least about 80%, 81%, 82%, 83%, 84%, more typically at least about 85%, 86%, 87%, 88%, 89%, more typically at least about 90%, 91%, 92%, 93%, 94%, and even more typically at least about 95%, 96%, 97%, 98%, 99% sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are nucleic acid sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences of SEQ ID NO: 1-84, or 168-251 or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, *e.g.* 15, 17, or 20 nucleotides or more that are selective for (*i.e.* specifically hybridize to) any one of the polynucleotides of the invention are contemplated. Probes capable of specifically hybridizing to a polynucleotide can differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequences provided in SEQ ID NO: 1-84, or 168-251, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NO: 1-84, or 168-251 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor or homology result for the nucleic acids of the present invention, including SEQ ID NO: 1-84, or 168-251, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST, which stands for Basic Local Alignment Search Tool, is used to search for local sequence alignments (Altschul, S.F. J Mol. Evol. 36 290-300 (1993))

and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm could also be used.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making
5 suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the
10 polynucleotides.

The nucleic acid sequences of the invention are further directed to sequences that encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the
15 location of the mutation and the nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations will typically be modified in series, *e.g.*, by
20 substituting first with conservative choices (*e.g.*, hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (*e.g.*, hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or
25 carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine
30 sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the
35 site of being changed. In general, the techniques of site-directed mutagenesis are well known to

those of skill in the art and this technique is exemplified by publications such as, Edelman et al., *DNA* 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, *Nucleic Acids Res.* 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids.

5 When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by the primer. The product DNA fragments replace the corresponding region in the plasmid and this
10 gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic
15 code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those that are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used
20 to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known
25 to those of skill in the art and can include, for example, methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO: 1-84, or 168-251, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct
30 the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, NY). Useful
35 nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g.,

plasmids, cosmids, lambda phage derivatives, phagemids, and the like, that are well known in the art. Accordingly, the invention also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell. Vectors according to the invention include expression
5 vectors, replication vectors, probe generation vectors, and sequencing vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid
10 having any of the nucleotide sequences of SEQ ID NO: 1-84, or 168-251 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of SEQ ID NO: 1-84, or 168-251 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of
15 the ORFs of the present invention, the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the ORF. Large numbers of suitable vectors and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors are provided by way of example. Bacterial: pBS, phagescript, PsiX174, pBluescript SK, pBS KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).
20

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al.,
25 *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector
30 or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt,
35 lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine

kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, *e.g.*, the ampicillin resistance gene of *E. coli* and *S. cerevisiae* TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), α -factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, *e.g.*, stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies

against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

5

3.2.1 ANTISENSE

Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1-84, or 168-251, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of a protein of any of SEQ ID NO: 85-167, or 252-335 or antisense nucleic acids complementary to a nucleic acid sequence of SEQ ID NO: 1-84, or 168-251 are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence of the invention. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence of the invention. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding a nucleic acid disclosed herein (*e.g.*, SEQ ID NO: 1-84, or 168-251), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of a mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of a mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of a mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified

nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used.

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a protein according to the invention to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res* 15: 6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res* 15: 6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett* 215: 327-330).

3.2.2 RIBOZYMES AND PNA MOIETIES

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as a mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave a mRNA transcripts to thereby inhibit translation of a mRNA. A ribozyme having specificity for a nucleic acid of the invention can be designed based upon the nucleotide sequence of a DNA disclosed herein (*i.e.*, SEQ ID NO: 1-84, or 168-251). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an mRNA of SEQ ID NO: 1-84, or 168-251 (see, *e.g.*, Cech *et al.* U.S. Pat. No. 4,987,071; and Cech *et al.* U.S. Pat. No. 5,116,742). Alternatively, polynucleotides of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region (*e.g.*, promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells. See generally, Helene. (1991) *Anticancer Drug Des.* 6: 569-84; Helene. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14: 807-15.

In various embodiments, the nucleic acids of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.* (1996) *Bioorg Med Chem* 4: 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under

conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996) above; Perry-O'Keefe *et al.* (1996) *PNAS* 93: 14670-675.

PNAs of the invention can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs of the invention can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup B. (1996) above); or as probes or primers for DNA sequence and hybridization (Hyrup *et al.* (1996), above; Perry-O'Keefe (1996), above).

In another embodiment, PNAs of the invention can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996) above). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996) above and Finn *et al.* (1996) *Nucl Acids Res* 24: 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA (Mag *et al.* (1989) *Nucl Acid Res* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.* (1996) above). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. See, Petersen *et al.* (1975) *Bioorg Med Chem Lett* 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci.* 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (See, *e.g.*, Krol *et*

al., 1988, *BioTechniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon, 1988, *Pharm. Res.* 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, etc.

5

3.3 HOSTS

The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection
10 methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell that drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or
15 increase, expression of endogenous polypeptide. Cells can be modified (*e.g.*, by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the polypeptide at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication
20 No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No. WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding
25 sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by
30 calcium phosphate transfection, DEAE, dextran mediated transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology* (1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., in *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts; described by Gluzman, *Cell* 23:175 (1981). Other cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial

strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent
5 attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used
10 to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences that affect the structure or stability of
15 the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences that alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, an enhancer that
25 has broader or different cell-type specificity than the naturally occurring elements can replace a tissue-specific enhancer. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The
30 identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable

marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques, which can be used in accordance with this aspect of the invention, are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

3.4 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO: 85-167, or 252-335 or an amino acid sequence encoded by any one of the nucleotide sequences SEQ ID NO: 1-84, or 168-251 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in SEQ ID NO: 1-84, or 168-251 or (b) polynucleotides encoding any one of the amino acid sequences set forth as SEQ ID NO: 85-167, or 252-335 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO: 85-167, or 252-335 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, 86%, 87%, 88%, 89%, at least about 90%, 91%, 92%, 93%, 94%, typically at least about 95%, 96%, 97%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO: 85-167, or 252-335.

Fragments of the proteins of the present invention that are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H. U. Saragovi, et al., *Bio/Technology* 10, 773-778 (1992) and in R. S. McDowell, et al., *J. Amer. Chem. Soc.* 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins. The protein coding sequence is identified in the sequence listing by translation of the disclosed nucleotide sequences. The mature form of such protein may be obtained by expression of a full-length
5 polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which it is expressed.

10 Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, *e.g.*, pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments that differ from a
15 nucleic acid fragment of the present invention (*e.g.*, an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid
20 sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments of larger polypeptides. Fragments are useful, for
25 example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells that have been altered to express the desired polypeptide or protein. As used herein, a cell
30 is said to be altered to express a desired polypeptide or protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell that produces one of the polypeptides or
35 proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable
5 expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

10 In an alternative method, the polypeptide or protein is purified from bacterial cells that naturally produce the polypeptide or protein. One skilled in the art can readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography,
15 and immuno-affinity chromatography. See, e.g., Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag (1994); Sambrook, et al., in *Molecular Cloning: A Laboratory Manual*; Ausubel et al., *Current Protocols in Molecular Biology*. Polypeptide fragments that retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein
20 domains.

The purified polypeptides can be used in *in vitro* binding assays that are well known in the art to identify molecules that bind to the polypeptides. These molecules include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist
25 activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to
30 cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO: 85-167, or 252-335.

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, *e.g.*, U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine, followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, Calif., U.S.A. (the MaxBat™ kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl™ or Cibacrom blue 3GA Sepharose™; one or more steps involving

hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form, which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX), or as a His tag. Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP- HPLC) steps employing hydrophobic RP-HPLC media, *e.g.*, silica gel having pendant methyl or other aliphatic groups can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, *e.g.*, targeting moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, *e.g.*, antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes, etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties, which may be fused to the polypeptide, include therapeutic agents that are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

3.4.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., *Nucleic Acids Research* 12(1):387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., *J. Mol. Biol.* 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., *Nucleic Acids Res.* vol. 25, pp. 3389-3402, herein incorporated by reference), eMATRIX software (Wu et al., *J. Comp. Biol.*, Vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, *ISMB-97*, Vol. 4, pp. 202-209, herein incorporated by reference), PFam software (Sonnhammer et al., *Nucleic Acids Res.*, Vol. 26(1), pp. 320-322 (1998), herein incorporated by reference), SignalP software package (Nielsen H et al., *Int. J. Neural Syst.*, Vol. 8, pp. 581 – 599 (1997), herein incorporated by reference) and the Kyte-Doolittle hydrophobicity prediction algorithm (*J. Mol. Biol.* 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., *J. Mol. Biol.* 215:403-410 (1990).

3.4.2 CHIMERIC AND FUSION PROTEINS

The invention also provides chimeric or fusion proteins. As used herein, a "chimeric protein" or "fusion protein" comprises a polypeptide of the invention operatively linked to another polypeptide. Within a fusion protein the polypeptide according to the invention can correspond to all or a portion of a protein according to the invention. In one embodiment, a fusion protein comprises at least one biologically active portion of a protein according to the invention. In another embodiment, a fusion protein comprises at least two biologically active portions of a protein according to the invention. Within the fusion protein, the term "operatively linked" is intended to indicate that the polypeptide(s) according to the invention and the other polypeptide(s) are fused in-frame to each other. The polypeptide can be fused to the N-terminus or C-terminus or in the middle.

For example, in one embodiment a fusion protein comprises a polypeptide according to the invention operably linked to the extracellular domain of a second protein.

In another embodiment, the fusion protein is a GST-fusion protein in which the polypeptide sequences of the invention are fused to the C-terminus of the GST (i.e., glutathione S-transferase) sequences.

In another embodiment, the fusion protein is an immunoglobulin fusion protein in which the polypeptide sequences according to the invention comprise one or more domains fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin

fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand and a protein of the invention on the surface of a cell, to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion proteins can be used to affect the bioavailability of a cognate ligand. Inhibition of the ligand/protein interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, *e.g.*, cancer as well as modulating (*e.g.*, promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used to bind and to dimerize 2 receptors and thereby transduce an intracellular signal. The immunoglobulin fusion proteins may also be used as immunogens to produce antibodies in a subject, to purify ligands, and in screening assays to identify molecules that inhibit the interaction of a polypeptide of the invention with a ligand.

A chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the protein of the invention.

3.5 GENE THERAPY

Mutations in the polynucleotides of the invention may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g.*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, Nature,

supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates (transient expression) or artificial chromosomes (stable expression). Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell, which drives expression of the polynucleotides in the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the desired protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to
5 replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences that affect the structure or stability of the RNA or
10 protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences that alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene
15 under the control of the new regulatory sequence, *e.g.*, inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally
20 occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the
25 property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial
30 xanthine-guanine phosphoribosyl-transferase (*gpt*) gene.

The gene targeting or gene activation techniques that can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436
35 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

3.6 TRANSGENIC ANIMALS

In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

3.7 USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the

polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or

5 polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or

10 indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation

15 or in one of the other physiological pathways described herein.

3.7.1 RESEARCH USES AND UTILITIES

The research community can use the polynucleotides provided by the present invention for various purposes. The polynucleotides can be used to express recombinant protein for

20 analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic

25 disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as

30 an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of

35 the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its
5 receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

10 Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch
15 and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

3.7.2 NUTRITIONAL USES

Polynucleotides and polypeptides of the present invention can also be used as nutritional
20 sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the
25 polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

3.7.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

30 A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one
35 or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient

confirmation of cytokine activity. The activity of therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK,

5 HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in
10 Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation,
15 Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin- γ , Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan. eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells
20 include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse
25 and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin
30 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in
35 Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W Strober,

Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

3.7.4 STEM CELL GROWTH FACTOR ACTIVITY

A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells *in vivo* or *ex vivo* is expected to maintain and expand cell populations in a totipotent or pluripotent state which would be useful for re-engineering damaged or diseased tissues, transplantation, manufacture of bio-pharmaceuticals and the development of bio-sensors. The ability to produce large quantities of human cells has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells, gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, bone marrow inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder

layer for the stem cell populations in culture or *in vivo*. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

Stem cells themselves can be transfected with a polynucleotide of the invention to induce
5 autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotent/pluripotent stem cell lines that are useful as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotent/pluripotent mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and
10 identification of differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be
15 used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In
20 addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a specific differentiated
25 cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., *Differentiation*, 48: 173-182, (1991); Klug et al., *J. Clin. Invest.*, 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering eds.* Lanza et al.,
30 Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

In vitro cultures of stem cells can be used to determine if the polypeptide of the invention
35 exhibits stem cell growth factor activity. Stem cells are isolated from any one of various cell

sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

3.7.5 HEMATOPOIESIS REGULATING ACTIVITY

A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/bone marrows (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In *Culture of Hematopoietic Cells*. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al.,
5 Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I. K. and Briddell, R. A. In *Culture of Hematopoietic Cells*. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., *Experimental Hematology* 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In *Culture of Hematopoietic Cells*. R. I. Freshney, et al. eds. Vol pp. 1-21,
10 Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R. I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In *Culture of Hematopoietic Cells*. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

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3.7.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

20

A polypeptide of the present invention that induces cartilage and/or bone growth in circumstances where bone is not normally formed has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De
25 novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of progenitors of
30 bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendonitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further, conditions that may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine,

kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

5 A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the
10 growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No.
15 WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

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3.7.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY

A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A
25 protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More
30 specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpes viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders that may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein (or antagonists thereof, including antibodies) of the present invention may also be useful in the treatment of allergic reactions and conditions (*e.g.*, anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by *in vivo* animal models such as the cumulative contact enhancement test (Lastbom et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxicol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process that requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue

transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be
5 sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

10 The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et
15 al., *Science* 257:789-792 (1992) and Turka et al., *Proc. Natl. Acad. Sci USA*, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., *Fundamental Immunology*, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune
20 diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self-tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of auto-reactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of
25 autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of auto-reactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine
30 experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., *Fundamental Immunology*, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means
35 of up regulating immune responses, may also be useful in therapy. Upregulation of immune

responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

5 Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected
10 cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

 A polypeptide of the present invention may provide the necessary stimulation signal to T
15 cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and β_2 microglobulin protein or an MHC class II alpha chain
20 protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as
25 the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

 The activity of a protein of the invention may, among other means, be measured by the
30 following methods:

 Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19;
35 Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA

78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Bowman et al., *J. Virology* 61:1992-1998; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Brown et al., *J. Immunol.* 153:3079-3092, 1994.

- 5 Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In *Current Protocols in Immunology*. J. E. e.a. Coligan eds. Vol 1
10 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

- Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3,
15 In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnolli et al., *J. Immunol.* 149:3778-3783, 1992.

- Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in:
20 Guery et al., *J. Immunol.* 134:536-544, 1995; Inaba et al., *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia et al., *Journal of Immunology* 154:5071-5079, 1995; Porgador et al., *Journal of Experimental Medicine* 182:255-260, 1995; Nair et al., *Journal of Virology* 67:4062-4069, 1993; Huang et al., *Science* 264:961-965, 1994; Macatonia et al., *Journal of Experimental Medicine* 169:1255-1264, 1989; Bhardwaj et al., *Journal of Clinical Investigation*
25 94:797-807, 1994; and Inaba et al., *Journal of Experimental Medicine* 172:631-640, 1990.

- Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., *Cytometry* 13:795-808, 1992; Gorczyca et al., *Leukemia* 7:659-670, 1993; Gorczyca et al., *Cancer Research*
30 53:1945-1951, 1993; Itoh et al., *Cell* 66:233-243, 1991; Zacharchuk, *Journal of Immunology* 145:4037-4045, 1990; Zamai et al., *Cytometry* 14:891-897, 1993; Gorczyca et al., *International Journal of Oncology* 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., *Blood* 84:111-117, 1994; Fine et

al., *Cellular Immunology* 155:111-122, 1994; Galy et al., *Blood* 85:2770-2778, 1995; Toki et al., *Proc. Nat. Acad. Sci. USA* 88:7548-7551, 1991.

3.7.8 ACTIVIN/INHIBIN ACTIVITY

A polypeptide of the present invention may also exhibit activin- or inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., *Endocrinology* 91:562-572, 1972; Ling et al., *Nature* 321:779-782, 1986; Vale et al., *Nature* 321:776-779, 1986; Mason et al., *Nature* 318:659-663, 1985; Forage et al., *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986.

3.7.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of

lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population.

- 5 Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

- 10 Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates
15 and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

20 3.7.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY

- A polypeptide of the invention may also be involved in hemostasis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events
25 in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

Therapeutic compositions of the invention can be used in the following:

- 30 Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

35 3.7.11 CANCER DIAGNOSIS AND THERAPY

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention
5 may indicate a hereditary risk of cancer, a precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

Cancer treatments promote tumor regression by inhibiting tumor cell proliferation,
10 inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma,
15 acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including
20 bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma,
25 tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Kaposi's sarcoma.

Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically
30 effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a
35 portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or

modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine.

Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide,

5 Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cis-DDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin, Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog),
10 Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

15 In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

20 *In vitro* models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These *in vitro* models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wiley-Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30
25 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available,
30 e.g. from American Type Tissue Culture Collection catalogs.

3.7.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the
35 invention can encode a polypeptide exhibiting such characteristics. Examples of such receptors

and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

10 The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

 Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1- 7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; 15 Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

 By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

 Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14. Examples of colorimetric molecules include, but are not limited to, fluorescent 25 molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin. 30

3.7.13 DRUG SCREENING

This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science* 282:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., *Mol. Biotechnol.* 9(3):205-23 (1998); Hruby et al., *Curr Opin Chem Biol*, 1(1):114-19 (1997); Dorner et al., *Bioorg Med Chem*, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

3.7.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules, that modulate (*i.e.*, increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) is then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s). As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a

protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

3.7.15 ANTI-INFLAMMATORY ACTIVITY

Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Compositions of this invention may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflammation associated with pulmonary disease, other autoimmune disease or inflammatory disease, an antiproliferative agent such as for acute or chronic myelogenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

3.7.16 LEUKEMIAS

Leukemias and related disorders may be treated or prevented by administration of a therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic

(granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

3.7.17 NERVOUS SYSTEM DISORDERS

- 5 Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of therapeutic utility, include but are not limited to nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of
- 10 neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:
- (i) traumatic lesions, including lesions caused by physical injury or associated with
 - 15 surgery, for example, lesions that sever a portion of the nervous system, or compression injuries;
 - (ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;
 - (iii) infectious lesions, in which a portion of the nervous system is destroyed or
 - 20 injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis;
 - (iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated
 - 25 with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;
 - (v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease,
 - 30 tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;
 - (vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;

(vii) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and

(viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

- (i) increased survival time of neurons in culture;
- (ii) increased sprouting of neurons in culture or *in vivo*;
- (iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
- (iv) decreased symptoms of neuron dysfunction *in vivo*.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, *etc.*, depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, *e.g.*, weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

3.7.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing
5 or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or
10 elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other
15 than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or
20 entity which is cross-reactive with such protein.

3.7.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis
25 and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving inflammation or immune response) or a differential response to drug administration, and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes
30 possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the
35 polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment

of genomic DNA, which may then be sequenced. Alternatively, the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition, traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of the protein, e.g., by an antibody specific to the variant sequence.

3.7.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis are determined in an experimental animal model system. The experimental model system is adjuvant induced arthritis in rats, and the protocol is described by J. Holoshitz, et al., 1983, Science, 219:56, or by B. Waksman et al., 1963, Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

3.8 THERAPEUTIC METHODS

The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

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3.8.1 EXAMPLE

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically, the amount of polypeptide administered per dose will be in the range of about 0.01 µg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1 µg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

3.9 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the

invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined
5 with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents that either enhance the
10 activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other
15 hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with
20 itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that
25 therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, e.g., treatment, healing, prevention or amelioration of the
30 relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or
35 simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

3.9.1 ROUTES OF ADMINISTRATION

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from

similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

3.9.2 COMPOSITIONS/FORMULATIONS

5 Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations that can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing,
10 dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered
15 in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil,
20 mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from
25 about 1 to 50% protein or other active ingredient of the present invention.

 When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other
30 active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or
35 other vehicle as known in the art. The pharmaceutical composition of the present invention may

also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from

pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*,

dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use

- 5 in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or
- 10 emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or

15 vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran.

Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

- 20 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be

25 formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- 30 A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system
- 35 (VPD:5W) consists of VPD diluted 1:1 with 5% dextrose in water solution. This co-solvent

system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B-lymphocytes will respond to antigen through their surface immunoglobulin receptor. T-lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified

MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

5 The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, 10 sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by reference.

 The amount of protein or other active ingredient of the present invention in the 15 pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments that the patient has undergone. Ultimately, the attending physician will decide the amount of protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention 20 and observe the patient's response. Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1 μ g to about 10 mg, more preferably about 25 0.1 μ g to about 1 mg) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention that are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable 30 form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention that may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or 35 sequentially with the composition in the methods of the invention. Preferably for bone and/or

cartilage formation, the composition would include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above-mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly (ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly (vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in

question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications.

5 Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, *e.g.*, amount of tissue weight desired to be formed, the site of
10 damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final
15 composition, may also affect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a
20 mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA). Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

25

3.9.3 EFFECTIVE DOSAGE

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount
30 effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate *in vitro* assays. For example, a dose can be formulated in animal models to achieve a
35 circulating concentration range that can be used to more accurately determine useful doses in

humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately determine useful doses in humans.

5 A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose
10 ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50} . Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may
15 vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, *e.g.*, Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain the
20 desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

 Dosage intervals can also be determined using MEC value. Compounds should be
25 administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

 An exemplary dosage regimen for polypeptides or other compositions of the invention
30 will be in the range of about 0.01 $\mu\text{g/kg}$ to 100 mg/kg of body weight daily, with the preferred dose being about 0.1 $\mu\text{g/kg}$ to 25 mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

5 3.9.4 PACKAGING

The compositions may, if desired, be presented in a pack or dispenser device that may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the
10 invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

3.10 ANTIBODIES

Also included in the invention are antibodies to proteins, or fragments of proteins of the
15 invention. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab} , $F_{ab'}$ and $F_{(ab')_2}$ fragments, and an F_{ab} expression library. In general, an antibody molecule obtained from
20 humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG₁, IgG₂, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

25 An isolated related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An
30 antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein, such as an amino acid sequence shown in SEQ ID NO: 85-167, or 252-335, and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least
35 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues.

Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of the protein that is located on the surface of the protein, *e.g.*, a hydrophilic region. A hydrophobicity analysis of the human related protein sequence will indicate which regions of a related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, *e.g.*, Hopp and Woods, 1981, *Proc. Nat. Acad. Sci. USA* 78: 3824-3828; Kyte and Doolittle 1982, *J. Mol. Biol.* 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, *Antibodies: A Laboratory Manual*, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

3.10.1 POLYCLONAL ANTIBODIES

For the production of polyclonal antibodies, various suitable host animals (*e.g.*, rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (*e.g.*, aluminum hydroxide), surface

active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

3.10.2 MONOCLONAL ANTIBODIES

The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can

be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and
5 thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego,
10 California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

15 The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the
20 art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting
25 dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such
30 as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using
35 oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and

light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

3.10.3 HUMANIZED ANTIBODIES

The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)).

3.10.4 HUMAN ANTIBODIES

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein.

5 Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using
10 human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991);
15 Marks et al., J. Mol. Biol., 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach
20 is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (Bio/Technology 10, 779-783 (1992)); Lonberg et al. (Nature 368 856-859 (1994)); Morrison (Nature 368, 812-13 (1994)); Fishwild et al. (Nature Biotechnology 14, 845-51 (1996)); Neuberger (Nature Biotechnology 14, 826 (1996)); and Lonberg and Huszar (Intern. Rev. Immunol. 13 65-93 (1995)).

25 Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins
30 are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the XenomouseTM
35 as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B

cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the

5 immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No.

10 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells

15 contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another

20 mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication

25 WO 99/53049.

3.10.5 F_{ab} FRAGMENTS AND SINGLE CHAIN ANTIBODIES

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778).

30 In addition, methods can be adapted for the construction of F_{ab} expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an F_{(ab)²}

35 fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated

by reducing the disulfide bridges of an $F_{(ab)2}$ fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

3.10.6 BISPECIFIC ANTIBODIES

5 Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the
10 recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct
15 bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion
20 preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable
25 host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the
30 CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for
35 increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (Fc R), such as Fc RI (CD64), Fc RII (CD32) and Fc RIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

3.10.7 HETEROCONJUGATE ANTIBODIES

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptopbutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

3.10.8 EFFECTOR FUNCTION ENGINEERING

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp Med.*, 176: 1191-1195 (1992) and Shopes, *J. Immunol.*, 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. *Cancer Research*, 53: 2560-2565 (1993). Alternatively, an antibody can

be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., *Anti-Cancer Drug Design*, 3: 219-230 (1989).

3.10.9 IMMUNOCONJUGATES

5 The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been
10 described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, *sapaonaria officinalis* inhibitor, gelonin,
15 mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP),
20 iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a
25 ricin immunotoxin can be prepared as described in Vitetta et al., *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such
30 streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

3.11 COMPUTER READABLE SEQUENCES

In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium that can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (*e.g.* text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NO: 1-84, or 168-251, or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any of the nucleotide sequences of SEQ ID NO: 1-84, or 168-251 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein-encoding fragments and may be useful in producing commercially important proteins

such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs that are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence that match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. Examples of such software include, but are not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration that is formed upon the folding of the target motif. There are a

variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

5

3.12 TRIPLE HELIX FORMATION

In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which methods are based on the binding of a polynucleotide sequence to DNA or RNA.

10 Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix-see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense-Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca
15 Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide.

20

3.13 DIAGNOSTIC ASSAYS AND KITS

The present invention further provides methods to identify the presence or expression of one of the ORFs of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention, optionally conjugated or otherwise associated
25 with a suitable label.

In general, methods for detecting a polynucleotide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polynucleotide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polynucleotide of the invention is detected in the sample. Such methods can also
30 comprise contacting a sample under stringent hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the invention under such conditions, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise contacting
35 a sample with a compound that binds to and forms a complex with the polypeptide for a period

sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of the antibodies or one or more of the nucleic acid probes of the present invention and assaying for
5 binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization,
10 amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice
15 and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or
20 extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention
25 provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate
30 containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container, which will accept the test
35 sample, a container, which contains the antibodies used in the assay, containers, which contain

wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers, which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats that are well known in the art.

3.14 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. No. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

3.15 SCREENING ASSAYS

Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide set forth in SEQ ID NO: 85-167, or 252-335 encoded by an ORF corresponding to any of the nucleotide sequences set forth in SEQ ID NO: 1-84, or 168-251, or which binds to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

- (a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and
- (b) determining whether the agent binds to said protein or said nucleic acid.

In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the

complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time
5 sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

Compounds identified via such methods can include compounds that modulate the
10 activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds that modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the
15 invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

20 For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can
25 readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspaczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

30 In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or
35 multiple ORFs that rely on the same EMF for expression control. One class of DNA binding

agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives that have base attachment capacity.

5 Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix-see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense-Okano, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca
10 Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

15 Agents that bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents that bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

20 3.16 USE OF NUCLEIC ACIDS AS PROBES

Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NO: 1-84, or 168-251. Because the corresponding gene is only expressed in
25 a limited number of tissues, a hybridization probe derived from any of the nucleotide sequences SEQ ID NO: 1-84, or 168-251 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample. Preferably a hybridization probe from any of nucleotide sequences SEQ ID NO: 1-84, or 168-251 can be used as an indicator of bone marrow tissue.

Any suitable hybridization technique can be employed, such as, for example, in situ
30 hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA

5 polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well-known genetic and/or chromosomal mapping techniques. These techniques include *in situ* hybridization, linkage analysis against known chromosomal markers, 10 hybridization screening with libraries or flow-sorted chromosomal preparations specific to known chromosomes, and the like. The technique of fluorescent *in situ* hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

Fluorescent *in situ* hybridization of chromosomal preparations and other physical 15 chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect 20 differences in gene sequences between normal, carrier or affected individuals.

3.17 PREPARATION OF SEQUENCING CHIPS AND ARRAYS

A basic example is using 6-mers attached to 50 micron surfaces to give a chip with dimensions of 3 x 3 mm which can be combined to give an array of 20 x 20 cm. Another 25 example is using 9-mer oligonucleotides attached to 10 x 10 microns surface to create a 9-mer chip, with dimensions of 5 x 5 mm. 4000 units of such chips may be used to create a 30 x 30 array. In an array in which 4,000 to 16,000 oligochips are arranged into a square array. A plate, or collection of tubes, as also depicted, may be packaged with the array as part of the sequencing kit.

30 The arrays may be separated physically from each other or by hydrophobic surfaces. One possible way to utilize the hydrophobic strip separation is to use technology such as the Iso-Grid Microbiology System produced by QA Laboratories, Toronto, Canada.

Hydrophobic grid membrane filters (HGMF) have been in use in analytical food microbiology for about a decade where they exhibit unique attractions of extended numerical 35 range and automated counting of colonies. One commercially available grid is ISO-GRID™

from QA Laboratories Ltd. (Toronto, Canada) which consists of a square (60 x 60 cm) of polysulfone polymer (Gelman Tuffryn HT-450, .45 μ m pore size) on which is printed a black hydrophobic ink grid consisting of 1600 (40 x 40) square cells. HGMF have previously been inoculated with bacterial suspensions by vacuum filtration and incubated on the differential or selective media of choice.

Because the microbial growth is confined to grid cells of known position and size on the membrane, the HGMF functions more like an MPN apparatus than a conventional plate or membrane filter. Peterkin et al. (1987) reported that these HGMFs can be used to propagate and store genomic libraries when used with a HGMF replicator. One such instrument replicates growth from each of the 1600 cells of the ISO-GRID and enables many copies of the master HGMF to be made (Peterkin et al., 1987).

Sharpe et al. (1989) also used ISO-GRID HGMF from QA Laboratories and an automated HGMF counter (MI-100 Interpreter) and RP-100 Replicator. They reported a technique for maintaining and screening many microbial cultures.

Peterkin and colleagues later described a method for screening DNA probes using the hydrophobic grid-membrane filter (Peterkin et al., 1989). These authors reported methods for effective colony hybridization directly on HGMFs. Previously, poor results had been obtained due to the low DNA binding capacity of the epoxysulfone polymer on which the HGMFs are printed. However, Peterkin et al. (1989) reported that the binding of the DNA to the surface of the membrane was improved by treating the replicated and incubated HGMF with polyethyleneimine, a polycation, prior to contact with DNA. Although this early work uses cellular DNA attachment, and has a different objective to the present invention, the methodology described may be readily adapted for Format 3 SBH.

In order to identify useful sequences rapidly, Peterkin et al. (1989) used radiolabeled plasmid DNA from various clones and tested its specificity against the DNA on the prepared HGMFs. In this way, DNA from recombinant plasmids was rapidly screened by colony hybridization against 100 organisms on HGMF replicates that can be easily and reproducibly prepared.

Manipulation with small (2-3 mm) chips, and parallel execution of thousands of the reactions. The solution of the invention is to keep the chips and the probes in the corresponding arrays. In one example, chips containing 250,000 9-mers are synthesized on a silicon wafer in the form of 8 x 8 mm plates (15 μ M/oligonucleotide, Pease et al., 1994) arrayed in 8 x 12 format (96 chips) with a 1 mm groove in between. Probes are added either by multichannel pipette or pin array, one probe on one chip. To score all 4000 6-mers, 42 chip arrays have to be used, either using different ones, or by reusing one set of chip arrays several times.

In the above case, using the earlier nomenclature of the application, F=9; P=6; and F+P=15. Chips may have probes of formula B_xN_n , where x is a number of specified bases B; and n is a number of non-specified bases, so that $x=4$ to 10 and $n=1$ to 4. To achieve more efficient hybridization, and to avoid potential influence of any support oligonucleotides, the specified bases can be surrounded by unspecified bases, thus represented by a formula such as $(N)_nB_x(N)_m$.

3.18 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata *et al.*, 1985; Dahlen *et al.*, 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller *et al.*, 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently bound to the microwell surface termed CovaLink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups ($>NH$) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the 5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA (Rasmussen *et al.*, (1991) Anal. Biochem. 198(1) 138-42).

The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen *et al.*, (1991). In this technology, a phosphoramidate bond is employed (Chu *et al.*, (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using

only a single covalent bond is preferred. The phosphoramidate bond joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via a phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm₇), is then added to a final concentration of 10 mM 1-MeIm₇. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well) standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm₇, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness *et al.* (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) Proc. Natl. Acad. Sci. USA 91(11) 5022-

6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

3.19 PREPARATION OF NUCLEIC ACID FRAGMENTS

The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook *et al.* (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer *et al.* (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, *Cvi*II, described by Fitzgerald *et al.* (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease *Cvi*II normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (*Cvi*II**), yield a quasi-random distribution of DNA fragments from the small molecule pUC19 (2688 base pairs). Fitzgerald *et al.* (1992) quantitatively evaluated the

randomness of this fragmentation strategy, using a *Cvi*II** digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that *Cvi*II** restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate
5 consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed

10 Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

15 3.20 PREPARATION OF DNA ARRAYS

Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the density of the wells is
20 achieved. One to 25 dots may be accommodated in 1 mm², depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may represent replica spotting of the same samples. In one example, a selected gene
25 segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane. Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm² and there may be a 1 mm space between subarrays.

30 Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments that are intended as illustrations of single aspects of the invention, and compositions and methods that are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations that should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

4.0 EXAMPLES

4.1 EXAMPLE 1

Novel Nucleic Acid Sequences Obtained From Various Libraries

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosomes using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences that flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones from each cluster were selected for sequencing.

The sequence of the amplified inserts, in some cases, was then deduced using a typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems (ABI) sequencer to obtain the novel nucleic acid sequences.

4.2 EXAMPLE 2

Novel Nucleic Acids

The novel nucleic acids of the present invention were assembled from sequences that were obtained from a cDNA library by methods described in Example 1 above, and in some cases sequences obtained from one or more public databases. The nucleic acids of SEQ ID NO: 1-84, inclusive, were assembled using an EST sequence as a seed. Then a recursive algorithm was used

to extend some of the seed ESTs into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 119, gb pri 119, and UniGene version 119, Geneseq October version, and Genscan, Genemark and Hyseq gene predictions on human genomic sequence from the human genome project updated October 2000) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

4.3 EXAMPLE 3

Further Characterization

Clusters from Example 1 were identified which were expressed in bone marrow tissue cDNA libraries, but not in other tissues. Novel nucleic acids were assembled by the method of Example 2. A subset of the assembled nucleic acids comprising sequences from the identified clusters was selected. This subset includes SEQ ID NO: 1-84. The tissue sources in which SEQ ID NO: 1-84 were exclusively expressed were found to be in BMD001 and BMD002 bone marrow libraries (Clontech).

The homologies for SEQ ID NO:1-84, and the corresponding peptide sequences, SEQ ID NO: 85-167, were obtained by performing various searches as shown in Tables 1A to 1D and as discussed herein.

The homologous sequences to the amino acid sequences corresponding to SEQ ID NO: 1-84 were obtained by a BLASTP version 2.0al 19MP-WashU search against the Geneseq database updated November 9, 2000, update 23 for year 2000 (Derwent), using the BLAST algorithm. The homologues for the amino acid sequences corresponding to SEQ ID NO: 1-84 from Geneseq are shown in Table 1A below.

The homologous sequences to the amino acid sequences corresponding to SEQ ID NO: 1-84 were also obtained by a BLASTP version 2.0al 19MP-WashU search against the NCBI Genbank nr database updated November 10, 2000, using the BLAST algorithm. The homologues for the amino acid sequences corresponding to SEQ ID NO: 1-84 from Genbank are shown in Table 1B below.

The homologous sequences to SEQ ID NO: 1-84 were also obtained by a BLASTN version 2.0al 19MP-WashU search against the Geneseq database updated November 9, 2000, update 23 for year 2000 (Derwent), using the BLAST algorithm. The homologues for SEQ ID NO: 1-84 from Geneseq are shown in Table 1C below.

The homologous sequences to SEQ ID NO: 1-84 were also obtained by a BLASTN version 2.0al 19MP-WashU search against the NCBI Genbank nt database updated November 10, 2000, using the BLAST algorithm. The homologues for SEQ ID NO: 1-84 from Genbank are shown in Table 1D below.

5 Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), the polypeptide sequences corresponding to SEQ ID NO: 1-84 were examined to determine whether they had identifiable signature regions. Table 2 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the
10 position(s) of the signature within the polypeptide sequence.

 Using the PFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences corresponding to SEQ ID NO: 1 – 84 were examined for domains with homology to certain peptide domains. Table 3 shows the name of the domain found, the description, the e-value and
15 the PFam score for the identified domain within the sequence.

 The polypeptide sequence within each of the polypeptides corresponding to SEQ ID NO: 1-84 that is the predicted signal peptide sequence and its cleavage site can be determined using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic
20 signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren Brunak, and Gunnar von Heijne in the publication “ Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites” Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A mean S score, as described in the Nielson et. al. was obtained for the polypeptide sequences. Table 4 shows the position of the
25 predicted signal peptide in each of the polypeptides corresponding to SEQ ID NO: 1-84 and the mean score associated with that signal peptide.

4.4 EXAMPLE 4

Assemblage of Novel Nucleic Acids

 The contigs or nucleic acids of the present invention, designated as SEQ ID NO: 168-251
30 were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 115, gb pri 115, and UniGene version 103 and exons from public domain genomic sequences predicted by Genscan) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above

databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

Table 6 sets forth the novel predicted polypeptides (including proteins) encoded by the novel polynucleotides (SEQ ID NO: 168-251) of the present invention, and their corresponding translation start and stop nucleotide locations to each of SEQ ID NO: 168-251. Table 6 also indicates the method by which the polypeptide was predicted. Method A refers to a polypeptide obtained by using a software program called FASTY (available from <http://fasta.bioch.virginia.edu>) which selects a polypeptide based on a comparison of the translated novel polynucleotide to known polynucleotides (W.R. Pearson, Methods in Enzymology, 183:63-98 (1990), herein incorporated by reference). Method B refers to a polypeptide obtained by using a software program called GenScan for human/vertebrate sequences (available from Stanford University, Office of Technology Licensing) that predicts the polypeptide based on a probabilistic model of gene structure/compositional properties (C. Burge and S. Karlin, J. Mol. Biol., 268:78-94 (1997), incorporated herein by reference). Method C refers to a polypeptide obtained by using a Hyseq proprietary software program that translates the novel polynucleotide and its complementary strand into six possible amino acid sequences (forward and reverse frames) and chooses the polypeptide with the longest open reading frame. These polynucleotides and polypeptides have homology to the sequences selected in Example 3.

Table 1A

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
1	T93038	1691 (259.8bits)	1.0e-70	93	T93038 Human monoclonal antibody light chain GM4-IgG4.lambda encoding DNA.
3	C10865	2666 (406.1bits)	9.0e-170	98	C10865 Human secreted protein 5' EST, SEQ ID NO: 14940. Length = 896
4	Q61170	1119 (173.9bits)	8.7e-45	97	Q61170 Human brain Expressed Sequence Tag EST01715. Length = 305
5	C06514	630 (100.6bits)	6.3e-45	100	C06514 Human secreted protein 5' EST, SEQ ID NO: 10589. Length = 741
7	C27831	2177 (332.7bits)	1.1e-90	99	C27831 Human secreted protein 5' EST, SEQ ID NO: 31906. Length = 442
8	Z13365	806 (127.0bits)	1.2e-30	99	Z13365 Human gene expression product cDNA sequence SEQ ID NO:834. Length = 300
10	T18679	588 (94.3bits)	2.1e-20	77	T18679 Human lastin cDNA (partial sequence). Length = 2223
11	Z65341	3392 (515.0bits)	1.3e-255	97	Z65341 Human secreted protein gene 92. Length = 1416
12	Q78896	2269 (346.5bits)	1.7e-97	99	Q78896 VHL disease gene g7. Length = 1816
13	Z97028	2999 (456.0bits)	2.5e-130	97	Z97028 Human secreted protein gene 10 cDNA clone HDPWU34, SEQ ID NO:20.
14	A46361	1943 (297.6bits)	1.0e-82	90	A46361 Nucleotide sequence of the gene insert of CINN 1. Length = 1549
15	A16623	3512 (533.0bits)	1.5e-236	73	A16623 Human secreted protein clone pt332_1 nucleotide sequence SEQ ID NO:11.
16	Z17710	3692 (560.0bits)	2.1e-161	98	Z17710 Human gene expression product cDNA sequence SEQ ID NO:5183. Length = 758
17	V84468	5332 (806.1bits)	0.0	95	V84468 Human secreted protein gene 58 clone HE9HU17. Length = 2483
18	C17456	345 (57.8bits)	1.5e-09	85	C17456 Human secreted protein 5' EST, SEQ ID NO: 21531. Length = 157
20	V57903	2178 (332.8bits)	1.0e-110	89	V57903 Hereditary haemochromatosis subregion from an HH affected individual.
21	X87150	5147	1.0e-227	98	X87150 Human protease

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
		(778.3bits)			HUPM-2 cDNA. Length = 3043
22	A45360	1189 (184.4bits)	4.9e-48	88	A45360 Mouse secreted expressed sequence tag SEQ ID NO:1935. Length = 374
23	C26801	1830 (280.6bits)	5.2e-77	96	C26801 Human secreted protein 5' EST, SEQ ID NO: 30876. Length = 393
24	Z16343	1930 (295.6bits)	7.9e-80	97	Z16343 Human gene expression product cDNA sequence SEQ ID NO:3813. Length = 465
25	X29140	6333 (956.3bits)	2.0e-281	72	X29140 Hypoxia-regulated gene sequence RTP220. Length = 4121
26	Z90631	6131 (925.9bits)	0.0	99	Z90631 Human adipose tissue protein #1 encoding DNA. Length = 3211
28	Z77502	1581 (243.3bits)	6.7e-66	84	Z77502 Human ovarian tumor cDNA library derived EST fragment 53. Length = 540
30	A58471	377 (62.6bits)	2.5e-07	55	A58471 Nucleotide sequence of the bleomycin (BLM) gene cluster ORFs 8-30.
32	X98701	3063 (465.6bits)	5.2e-132	95	X98701 Human validated cancer cell derived cDNA #23. Length = 750
33	V34159	1317 (203.7bits)	3.5e-53	89	V34159 Human secreted protein gene 6 clone HBMCY91. Length = 425
34	X34656	1275 (197.4bits)	1.1e-52	66	X34656 Human ZIP-kinase (serine/threonine kinase) encoding DNA. Length = 2132
36	C08395	580 (93.1bits)	1.4e-20	79	C08395 Human secreted protein 5' EST, SEQ ID NO: 12470. Length = 406
40	X37471	400 (66.1bits)	7.4e-19	100	X37471 Human secreted protein cDNA fragment containing gene 21. Length = 990
41	T22028	487 (79.1bits)	7.3e-16	95	T22028 Human gene signature HUMGS03571. Length = 127
42	Z94751	447 (73.1bits)	2.1e-12	57	Z94751 Human ATP binding cassette ABCA8 (ABC-new) cDNA. Length = 2911
43	C31590	1353 (209.1bits)	1.7e-55	98	C31590 Human secreted protein 5' EST, SEQ ID NO: 35665. Length = 417
44	C02717	1313 (203.1bits)	1.7e-53	98	C02717 Human secreted protein 5' EST, SEQ ID NO: 2715.

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
					Length = 268
45	Z87318	385 (63.8bits)	9.9e-08	57	Z87318 <i>S. venezuelae</i> pik (macrolide biosynthesis) gene cluster. Length = 36,778
46	V12391	383 (63.5bits)	5.9e-09	64	V12391 Mouse osteoclast transporter protein encoding cDNA. Length = 2102
47	Z16086	318 (53.8bits)	3.2e-06	59	Z16086 Human gene expression product cDNA sequence SEQ ID NO:3556. Length = 754
48	V32401	1467 (226.2bits)	1.7e-60	99	V32401 Homo sapiens spry3 gene. Length = 300
50	C26006	996 (155.5bits)	4.6e-39	98	C26006 Human secreted protein 5' EST, SEQ ID NO: 30081. Length = 208
60	C09439	913 (143.0bits)	2.4e-35	94	C09439 Human secreted protein 5' EST, SEQ ID NO: 13514. Length = 222
71	C27703	640 (102.1bits)	2.7e-23	73	C27703 Human secreted protein 5' EST, SEQ ID NO: 31778. Length = 431
82	C32463	177 (32.6bits)	4.1e-07	94	C32463 Human secreted protein 5' EST, SEQ ID NO: 36538. Length = 100

Table 1B

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
1	L29164.1	2253 (344.1bits)	3.5E-95	96	HUMIGLZF Human immunoglobulin light chain variable region (lambda-IIIb subgroup) from IgM rheumatoid factor
2	AF305057.1	2236 (341.5bits)	1.4E-93	98	"AF305057 Homo sapiens RTS (RTS) gene, complete cds, alternatively spliced"
3	X52851.1	1092 (169.9bits)	6.9E-143	82	HSCPH70 Human cyclophilin gene for cyclophilin (EC 5.2.1.8) Length = 6711
4	L21936.1	2302 (351.4bits)	4.2E-102	96	"HUMSDHX Human succinate dehydrogenase flavoprotein subunit (SDH) mRNA, complete cds"
5	AL033529.2 5	681 (108.2bits)	1.6E-46	98	"HS2705 Human DNA sequence from clone RP1-2705 on chromosome 1p34.1-35.3, complete sequence [Homo sapiens]"
6	AL121601.1 3	1097 (170.6bits)	3.6E-94	98	"HSDJ315G1 Human DNA sequence from clone RP1-315G1 on chromosome Xq24-25. Contains a PDZ (DHR, GLGF) domain protein"
7	AL162331.1	33983 (5104.9bits)	0.0	98	HS118D241 Novel human gene mapping to chromosome 1 Length = 6941
8	AK023176. 1	5874 (887.4bits)	1.8E-259	99	"AK023176 Homo sapiens cDNA FLJ13114 fis, clone NT2RP3002603 Length = 2730"
9	AB037855. 1	5253 (794.2bits)	0.0	93	"AB037855 Homo sapiens mRNA for KIAA1434 protein, partial cds Length = 5443"
10	AC004890. 2	617 (98.6bits)	2E-20	94	"AC004890 Homo sapiens PAC clone RP4-800G7 from 7q35-q36, complete sequence"
11	AB020653. 1	5341 (807.4bits)	0.0	97	"AB020653 Homo sapiens mRNA for KIAA0846 protein, complete cds Length = 4204"
12	AC007999. 11	1914 (293.2bits)	9.1E-144	96	AC007999 Homo sapiens 3q25-26 BAC CTB-177N7 (California Institute of Technology BAC Library) complete sequence

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
13	AB020598.1	6253 (944.3bits)	1.7E-276	98	"AB020598 Homo sapiens mRNA for peptide transporter 3, complete cds"
14	AF153607.1	1995 (305.4bits)	8.2E-84	91	"AF153607 Homo sapiens px19 mRNA, complete cds Length = 943"
15	AB032996.1	12529 (1885.9bits)	0.0	99	"AB032996 Homo sapiens mRNA for KIAA1170 protein, partial cds Length = 5073"
16	AB033007.1	12151 (1829.2bits)	0.0	99	"AB033007 Homo sapiens mRNA for KIAA1181 protein, partial cds Length = 2432"
17	AL117430.1	5341 (807.4bits)	7.7E-293	95	HSM800939 Homo sapiens mRNA; cDNA DKFZp434D156 (from clone DKFZp434D156); partial cds
18	AL357654.9	685 (108.8bits)	1.6E-23	100	"AL357654 Human DNA sequence from clone RP5-1025P18 on chromosome 20 Contains ESTs, STSs and GSSs, complete sequence [Homo]"
19	AB020677.2	15274 (2297.8bits)	0.0	99	"AB020677 Homo sapiens mRNA for KIAA0870 protein, partial cds Length = 4628"
20	AC009505.3	2855 (434.4bits)	8.5E-201	89	"AC009505 Homo sapiens BAC clone RP11-526D2 from 2, complete sequence"
21	AF206019.1	15735 (2366.9bits)	0.0	99	"AF206019 Homo sapiens REV1 protein (REV1) mRNA, complete cds Length = 4276"
22	8923709 ref	1547 (238.2bits)	1.7E-63	93	NM_017548.1
23	Z83840.7	4939 (747.1bits)	1.2E-215	85	HS216E10 Human DNA sequence from clone CTA-216E10 on chromosome 22 Contains the NHP2L1 gene for non-histone chromosome protein 2
24	AB028958.1	15904 (2392.3bits)	0.0	98	"AB028958 Homo sapiens mRNA for KIAA1035 protein, partial cds Length = 5124"
25	AF273437.1	16890 (2540.2bits)	0.0	100	"AF273437 Homo sapiens actin binding protein anillin mRNA, complete cds"
26	AB011792.1	6121 (924.4bits)	0.0	99	"AB011792 Homo sapiens mRNA for extracellular matrix protein, complete cds"
27	AF130358.2	2233	1.1E-105	97	"AF130358 Homo sapiens

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
		(341.1bits)			chromosome 21q11.2 PAC 90B5, complete sequence"
28	AC009289.8	2003 (306.6bits)	6E-108	96	"AC009289 Homo sapiens, clone RP11-44J3, complete sequence Length = 146,010"
29	AC007386.3	1768 (271.3bits)	1.2E-116	94	"AC007386 Homo sapiens BAC clone RP11-359K10 from 2, complete sequence"
30	AK024129.1	795 (125.3bits)	1.5E-25	97	"AK024129 Homo sapiens cDNA FLJ14067 fis, clone HEMBB1001315 Length = 4153"
31	AC007999.11	795 (125.3bits)	4.9E-116	79	AC007999 Homo sapiens 3q25-26 BAC CTB-177N7 (California Institute of Technology BAC Library) complete sequence
32	AB037825.1	28786 (4325.1bits)	0.0	98	"AB037825 Homo sapiens mRNA for KIAA1404 protein, partial cds Length = 7204"
33	AB023218.1	12029 (1810.9bits)	0.0	98	"AB023218 Homo sapiens mRNA for KIAA1001 protein, complete cds Length = 4304"
34	AB007144.1	1275 (197.4bits)	1.2E-51	66	"AB007144 Homo sapiens mRNA for ZIP-kinase, complete cds Length = 2105"
35	AC006241.1	1031 (160.7bits)	6.9E-48	99	"AC006241 Homo sapiens chromosome 9, clone hRPK.202_H_3, complete sequence"
36	AC008733.7	759 (119.9bits)	7.7E-27	96	"AC008733 Homo sapiens chromosome 19 clone CTD-2525J15, complete sequence"
37	AF026813.1	1627 (250.2bits)	2.4E-67	92	AF026813 Homo sapiens topoisomerase III gene promoter region Length = 1361
38	AK022932.1	3459 (525.0bits)	2.3E-191	99	"AK022932 Homo sapiens cDNA FLJ12870 fis, clone NT2RP2003727 Length = 2566"
40	AF161365.1	2726 (415.1bits)	1.4E-116	99	"AF161365 Homo sapiens HSPC102 mRNA, partial cds Length = 547"
41	AL121934.17	687 (109.1bits)	5.5E-41	73	HSBA209A2 Human DNA sequence from clone RP11-209A2 on chromosome 6. Contains an RPL10 (60S ribosomal protein L10)

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
42	AF250238.1	447 (73.1bits)	2.6E-11	57	"AF250238 Homo sapiens macrophage ABC transporter (ABCA7) mRNA, complete cds"
43	AB046641.1	2389 (364.5bits)	1E-181	97	"AB046641 Macaca fascicularis brain cDNA, clone QccE-16161 Length = 2901"
44	AL365224.8	2296 (350.5bits)	9E-107	99	"AL365224 Human DNA sequence from clone RP11-96B21 on chromosome 6, complete sequence [Homo sapiens]"
45	AF168787.1	12094 (1820.6bits)	0.0	99	"AF168787 Homo sapiens vanilloid receptor gene, partial sequence; CARKL and CTNS genes, complete cds; TIP1 gene, partial cds; P2X5b"
46	AC000353.27	821 (129.2bits)	1.2E-29	77	"AC000353 Homo sapiens Chromosome 11q13 BAC Clone 18h3, complete sequence"
47	U37263.1	522 (84.4bits)	2E-16	64	"HSU37263 Human KRAB zinc finger protein (ZNF177) mRNA, complete cds"
48	AJ271735.1	7131 (1076.0bits)	0.0	99	"HSA271735 Homo sapiens Xq pseudoautosomal region; segment 1/2 Length = 240,000"
50	L22009.1	576 (92.5bits)	1.9E-16	79	"HUM49KDA Human hnRNP H mRNA, complete cds Length = 2201"
51	AF249738.1	1537 (236.7bits)	1.8E-63	73	AF249738 Mus musculus Pb99 gene sequence Length = 2127
55	AL138994.3	366 (61.0bits)	0.0000024	57	CNS01DWZ Human chromosome 14 DNA sequence *** IN PROGRESS *** BAC C-2046P20 of library CalTech-D from chromosome 14 of Homo
59	AC010137.3	1325 (204.9bits)	2.7E-112	100	"AC010137 Homo sapiens BAC clone RP11-169D1 from Y, complete sequence"
60	AK024343.1	2098 (320.8bits)	7.5E-89	90	"AK024343 Homo sapiens cDNA FLJ14281 fis, clone PLACE1005611, weakly similar to Mus musculus mRNA for mDj10"
62	AL034375.2	1140	4E-65	97	HS523G1 Human DNA

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
	3	(177.1bits)			sequence from clone 523G1 on chromosome 6p22.3-24.1 Contains part of the mRNA for SCA1 (spinocerebellar)
65	AC005740.1	3048 (463.4bits)	3.1E-130	99	"AC005740 Homo sapiens chromosome 5p, BAC clone 50g21 (LBNL H154), complete sequence"
69	AL135783.6	1648 (253.3bits)	5.4E-67	99	"AL135783 Human DNA sequence from clone RP3-527F8 on chromosome Xq25-27.1, complete sequence [Homo sapiens]"
70	AL049715.2 5	1824 (279.7bits)	2.7E-87	93	"HSJ646P11 Human DNA sequence from clone RP4-646P11 on chromosome 1, complete sequence [Homo sapiens]"
71	AC006157.2	1801 (276.3bits)	6.6E-74	99	"AC006157 Homo sapiens BAC clone RP11-414C23 from Y, complete sequence"
75	AC016622.5	688 (109.3bits)	1.2E-23	90	"AC016622 Homo sapiens chromosome 5 clone CTD-2343F18, complete sequence"
78	AC010627.5	3031 (460.8bits)	1.8E-129	98	"AC010627 Homo sapiens chromosome 5 clone CTD-2165H16, complete sequence"
79	AL132822.1 5	1257 (194.6bits)	2.5E-49	99	"HSJ1017F8 Human DNA sequence from clone RP5-1017F8 on chromosome 20 Contains STSs, GSSs and a CpG Island, complete"
80	AC012315.5	1150 (178.6bits)	1.7E-44	100	"AC012315 Homo sapiens chromosome 5 clone CTD-2122K7, complete sequence"
82	AC026425.3	1196 (185.5bits)	1.4E-46	99	"AC026425 Homo sapiens chromosome 5 clone CTD-2183D23, complete sequence"
83	AP001331.1	2020 (309.1bits)	8.5E-84	100	"AP001331 Homo sapiens genomic DNA, chromosome 8q23, clone:KB1153C10"

Table 1C

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
1	W34081	374 (136.7bits)	1.6e-34	85	W34081 Human monoclonal antibody light chain GM4-IgG4.lambda. Length = 129
3	G03831	104 (41.7bits)	6.6e-06	39	G03831 Human secreted protein, SEQ ID NO: 7912. Length = 165
9	G46687	196 (74.1bits)	3.8e-15	29	G46687 Arabidopsis thaliana protein fragment SEQ ID NO: 58762. Length = 374
10	R94903	136 (52.9bits)	3.9e-08	52	R94903 Human lastin. Length = 675
11	Y70963	687 (246.9bits)	7.2e-70	51	Y70963 Human Ras signalling pathway associated protein CalDAG-GEFII. Length = 797
12	R66286	304 (112.1bits)	4.2e-27	100	R66286 VHL disease gene g7 product. Length = 284
13	G16993	169 (64.5bits)	2.1e-10	31	G16993 Arabidopsis thaliana protein fragment SEQ ID NO: 17846. Length = 464
15	Y94903	1182 (421.1bits)	3.8e-120	59	Y94903 Human secreted protein clone pt332_1 protein sequence SEQ ID NO:12.
16	G33308	291 (107.5bits)	2.3e-39	35	G33308 Zea mays protein fragment SEQ ID NO: 40339. Length = 350
17	W88812	143 (55.4bits)	3.7e-09	39	W88812 Polypeptide fragment encoded by gene 58. Length = 452
19	R90766	178 (67.7bits)	2.3e-09	24	R90766 Tumour suppressor protein HTS-1. Length = 1137
20	R76595	118 (46.6bits)	2.2e-07	27	R76595 MoMLV mutated gag matrix protein. Length = 131
21	G48221	286 (105.7bits)	5.0e-38	43	G48221 Arabidopsis thaliana protein fragment SEQ ID NO: 60872. Length = 1114
24	Y13055	183 (69.5bits)	3.9e-14	97	Y13055 Human secreted protein encoded by 5' EST SEQ ID NO: 69. Length = 39
25	Y03636	3020 (1068.2bits) 6.5e-315	6.5e-315	71	Y03636 Hypoxia-regulated gene RTP220 product. Length = 864
26	Y67598	1051 (375.0bits)	2.9e-106	99	Y67598 Human adipose tissue protein #1. Length = 699
28	Y76628	143 (55.4bits)	4.8e-10	56	Y76628 Human ovarian tumor EST fragment encoded protein 124. Length = 94
33	W75062	359 (131.4bits)	6.2e-33	93	W75062 Human secreted protein encoded by gene 6 clone

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
					HBMCY91. Length = 73
34	Y06921	267 (99.0bits)	9.7e-23	39	Y06921 Human ZIP-kinase (serine/threonine kinase). Length = 454
39	W81727	127 (49.8bits)	1.8e-07	41	W81727 M. tuberculosis immunogenic polypeptide TbH-30. Length = 174
43	G02019	128 (50.1bits)	2.0e-07	38	G02019 Human secreted protein, SEQ ID NO: 6100. Length = 82
44	G02711	411 (149.7bits)	1.9e-38	97	G02711 Human secreted protein, SEQ ID NO: 6792. Length = 81
46	W44195	116 (45.9bits)	4.0e-06	42	W44195 Mouse osteoclast transporter protein. Length = 537
48	W48792	643 (231.4bits)	5.0e-63	46	W48792 Homo sapiens sprouty 2 protein. Length = 315
49	Y32167	184 (69.8bits)	2.2e-14	59	Y32167 Soybean E2F protein fragment. Length = 80
60	Y91941	145 (56.1bits)	1.6e-09	43	Y91941 Human chaperone protein 2 (HCHP-2). Length = 375

Table 1D

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
1	AAA66494.1	413 (150.4bits)	2.0e-38	89	(L29164) immunoglobulin light chain variable region [Homo sapiens]
3	CSRT31	140 (54.3bits)	1.7e-09	58	CSRT31 protein P31 - rat >prf
5	AAF55906.1	141 (54.7bits)	1.3e-09	69	(AE003735) CG6353 gene product [Drosophila melanogaster] Length = 156
7	CAB82724.1	5366 (1894.0bits)	0.0	97	(AL162331) hypothetical protein [Homo sapiens] Length = 2270
8	BAB14447.1	900 (321.9bits)	5.0e-90	98	(AK023176) unnamed protein product [Homo sapiens] Length = 265
9	BAA92672.1	1305 (464.4bits)	6.0e-133	99	(AB037855) KIAA1434 protein [Homo sapiens] >emb
10	AAD45827.1	132 (51.5bits)	1.2e-08	80	AC004890_4 (AC004890) similar to zinc finger proteins; similar to BAA24380 [Homo sapiens]
11	NP_056191.1	1292 (459.9bits)	1.4e-131	91	KIAA0846 protein [Homo sapiens] >dbj BAA74869.1 (AB020653) KIAA0846 protein [Homo sapiens]
12	BAB14132.1	759 (272.2bits)	4.3e-75	97	(AK022613) unnamed protein product [Homo sapiens] Length = 664
13	NP_057666.1	957 (341.9bits)	4.5e-96	100	peptide transporter 3 [Homo sapiens] >dbj BAA93432.1 (AB020598) peptide transporter 3 [Homo sapiens]
15	BAA86484.1	2104 (745.7bits)	1.3e-217	99	(AB032996) KIAA1170 protein [Homo sapiens] Length = 838
16	BAA86495.1	1545 (548.9bits)	2.2e-158	100	(AB033007) KIAA1181 protein [Homo sapiens] Length = 336
17	NP_056345.1	143 (55.4bits)	4.7e-09	39	DKFZP434156 protein
19	BAA74893.2	5332 (1882.0bits)	0.0	99	(AB020677) KIAA0870 protein [Homo sapiens] Length = 1019
20	GAG_AVIS N	160 (61.4bits)	3.7e-11	42	GAG_AVISN GAG POLYPROTEIN [CONTAINS: CORE PROTEIN P15; INNER COAT PROTEIN P12; CORE SHELL

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
					PROTEIN P30] >pir
21	NP_057400.1	2952 (1044.2bits)	1.8e-307	100	REV1 protein [Homo sapiens] >gb AAF06731.1 AF151538_1 (AF151538) deoxycytidyl transferase;
22	NP_060018.1	385 (140.6bits)	1.9e-35	100	hypothetical protein [Homo sapiens] >gb AAF02423.1 AF103803_1 (AF103803) unknown [Homo sapiens]
23	AAG00552.1	164 (62.8bits)	4.5e-09	25	AF286473_1 (AF286473) retinitis pigmentosa GTPase regulator [Mus musculus]
24	NP_056054.1	1355 (482.0bits)	3.0e-138	100	KIAA1035 protein [Homo sapiens] >dbj BAA91749.1 (AK001544) unnamed protein product [Homo sapiens]
25	NP_061155.1	5727 (2021.1bits)	0.0	100	anillin [Homo sapiens] >gb AAF75796.1 AF273437_1 (AF273437) actin binding protein anillin [Homo sapiens]
26	NP_001384.1	1051 (375.0bits)	4.9e-106	99	extracellular matrix protein 2 [Homo sapiens] >dbj BAA33958.1 (AB011792) extracellular matrix protein [Homo
30	AAF48140.2	168 (64.2bits)	4.5e-08	26	(AE003488) CG2779 gene product [Drosophila melanogaster] Length = 1612
31	B71413	194 (73.4bits)	7.2e-15	39	B71413 hypothetical protein dl3525w - Arabidopsis thaliana >emb
32	BAA92102.1	1661 (589.8bits)	1.1e-170	90	(AK002139) unnamed protein product [Homo sapiens] Length = 893
33	NP_055775.1	759 (272.2bits)	4.3e-75	96	KIAA1001 protein [Homo sapiens] >dbj BAA76845.1 (AB023218) KIAA1001 protein [Homo sapiens]
34	NP_001339.1	267 (99.0bits)	1.6e-22	39	death-associated protein kinase 3 [Homo sapiens] >dbj BAA24955.1 (AB007144) ZIP-kinase [Homo sapiens]
38	BAB14313.1	571 (206.1bits)	1.6e-81	94	(AK022932) unnamed protein product [Homo sapiens] Length = 838
39	A56154	149 (57.5bits)	5.9e-07	28	A56154 Abl substrate ena (enabled) - fruit fly

SEQ ID NO:	Accession No	Blast Score	p-value	% Identity	Description
					(Drosophila melanogaster) >gb
43	BAB03558.1	582 (209.9bits)	2.5e-56	79	(AB046640) hypothetical protein [Macaca fascicularis] Length = 740
45	BAB00640.1	679 (244.1bits)	1.3e-66	50	(AB036930) hapsin [Mus musculus] Length = 754
46	CAB09724.1	120 (47.3bits)	2.7e-06	46	(Z97028) renal organic anion transporter [Pseudopleuronectes americanus]
47	AAB09748.1	133 (51.9bits)	9.4e-09	39	(U37251) Description: KRAB zinc finger protein; this is a splicing variant that contains a stop codon and frame shift between
48	CAB96768.1	1586 (563.4bits)	1.0e-162	100	(AJ271735) sprouty (Drosophila) homolog 3 [Homo sapiens] Length = 288
49	CAC01815.1	199 (75.1bits)	2.5e-15	42	(AL391146) E2F transcription factor-like protein [Arabidopsis thaliana]
60	NP_060096.1	145 (56.1bits)	2.7e-09	43	hypothetical protein FLJ20027 [Homo sapiens] >dbj BAA90896.1 (AK000034) unnamed protein product [Homo sapiens]

TABLE 2

SEQ ID NO:	Accession No:	Description	p-value	Raw Score	Residue Position
9	PD01922B	PROTEIN PHOSPHODIEST ERASE HYDROL.	8.714E-20	21.83	63-99
13	BL01022B	PTR2 family proton/o ligo peptide symporters proteins	6.016E-14	22.19	72-118
13	BL01022A	PTR2 family proton/o ligo peptide symporters proteins	9.135E-12	11.58	42-61
13	PR00490A	SECRETIN RECEPTOR SIGNATURE	6.889E-09	4.58	191-204
20	PF01140A	Matrix protein (MA), P15	2.274E-12	11.51	1-55
26	BL01208B	VWFC domain proteins	1.0E-13	15.83	7-22
26	BL00422C	Granins proteins.	5.765E-09	16.18	132-160
26	BL00422C	Granins proteins.	7.706E-09	16.18	126-154
28	PR00234B	HIV-1 MATRIX PROTEIN SIGNATURE	7.25E-09	17.94	108-127
30	PD00787B	SYNTHASE BIOSYNTHESIS SIGNATURE	8.085E-09	13.26	792-806
33	BL00523A	Sulfatases proteins.	7.5E-17	13.36	36-53
33	BL00523C	Sulfatases proteins.	6.143E-14	12.64	129-140
33	BL00523B	Sulfatases proteins.	8.105E-14	8.64	84-96
48	PR00614A	NI-FE HYDROGENASE SMALL SUBUNIT SIGNATURE	8.373E-09	13.66	159-182
49	PD02910A	TRANSCRIPTION PROTEIN FACTOR REGULATION A.	7.0E-16	15.43	146-181
52	PR00209B	ALPHA/BETA GLIADIN FAMILY SIGNATURE	9.906E-09	4.88	124-143
58	BL01166F	RNA polymerases beta chain protiens	6.049E-09	7.27	175-186
60	PR00625B	DNAJ PROTEIN FAMILY SIGNATURE	1.321E-13	13.48	33-54
60	BL00636B	Nt-dnaJ domain proteins	8.333E-13	15.11	33-54

TABLE 3

SEQ ID NO:	pFam model name	Accession No:	Predicted beginning of domain	Predicted end of domain	pfam Score	e-value
1	ig	PF01812	9	65	16	0.0022
3	pro_isomerase	PF00160	62	78	8.6	0.22
10	KRAB	PF01352	4	34	-12.7	0.29
11	RasGEF	PF00617	146	308	-13	1.10E-05
12	VHL	PF01847	159	217	149.4	6.50E-41
13	PTR2	PF00854	101	185	9.2	0.06
19	DENN	PF02141	117	223	84.8	1.60E-22
19	TPR	PF01365	489	522	10.5	3.6
19	WD40	PF00400	867	904	12.3	1.3
19	WD40	PF00400	908	949	14	0.8
19	WD40	PF00400	1089	1128	6.1	8.7
20	gag_MA	PF01140	2	68	42.2	3.30E-11
21	BRCT	PF00533	44	131	57.3	3.30E-13
21	ODC_AZ	PF02100	333	355	2.2	8.2
25	PH	PF01636	985	1108	60.2	2.00E-15
48	metalthio	PF00131	121	191	-10.5	6.9
51	hormone	PF00103	16	25	1.1	4.7
60	DnaJ	PF00226	23	56	-0.8	0.032

TABLE 4

SEQ ID NO:	Signal peptides position	Mean Score	Cutoff	Conclusion
1	1-55	0.108	0.48	NO
2	1-9	0.116	0.48	NO
3	1-10	0.166	0.48	NO
4	1-143	0.16	0.48	NO
5	1-16	0.135	0.48	NO
6	1-8	0.104	0.48	NO
7	1-746	0.077	0.48	NO
8	1-31	0.63	0.48	YES
9	1-221	0.062	0.48	NO
10	1-22	0.075	0.48	NO
11	1-299	0.117	0.48	NO
12	1-89	0.252	0.48	NO
13	1-177	0.462	0.48	NO
14	1-73	0.458	0.48	NO
15	1-268	0.186	0.48	NO
16	1-46	0.447	0.48	NO
17	1-130	0.119	0.48	NO
18	1-36	0.278	0.48	NO
19	1-508	0.157	0.48	NO
20	1-6	0.293	0.48	NO
21	1-258	0.052	0.48	NO
22	1-37	0.095	0.48	NO
23	1-71	0.036	0.48	NO
24	1-96	0.115	0.48	NO
25	1-623	0.051	0.48	NO
26	1-38	0.125	0.48	NO
27	1-63	0.068	0.48	NO
28	1-14	0.221	0.48	NO
29	1-42	0.402	0.48	NO
30	1-724	0.096	0.48	NO
31	1-150	0.083	0.48	NO
32	1-284	0.103	0.48	NO
33	1-16	0.895	0.48	YES
34	1-136	0.062	0.48	NO
35	1-43	0.233	0.48	NO
36	1-146	0.073	0.48	NO
37	1-66	0.072	0.48	NO
38	1-150	0.253	0.48	NO
39	1-115	0.077	0.48	NO
40	1-79	0.137	0.48	NO
41	1-16	0.914	0.48	YES
42	1-83	0.211	0.48	NO
43	1-132	0.198	0.48	NO
44	1-94	0.059	0.48	NO
45	1-463	0.093	0.48	NO
46	1-61	0.168	0.48	NO
47	1-131	0.094	0.48	NO

SEQ ID NO:	Signal peptides position	Mean Score	Cutoff	Conclusion
48	1-237	0.156	0.48	NO
49	1-77	0.053	0.48	NO
50	1-8	0.274	0.48	NO
51	1-126	0.085	0.48	NO
52	1-37	0.61	0.48	YES
53	1-24	0.551	0.48	YES
54	1-24	0.548	0.48	YES
55	1-77	0.182	0.48	NO
56	1-25	0.55	0.48	YES
57	1-127	0.086	0.48	NO
58	1-89	0.152	0.48	NO
59	1-15	0.702	0.48	YES
60	1-41	0.045	0.48	NO
61	1-61	0.071	0.48	NO
62	1-104	0.163	0.48	NO
63	1-34	0.622	0.48	YES
64	1-36	0.685	0.48	YES
65	1-18	0.226	0.48	NO
66	1-51	0.453	0.48	NO
67	1-51	0.067	0.48	NO
68	1-11	0.064	0.48	NO
69	1-0	0	0.48	NO
70	1-23	0.347	0.48	NO
71	1-43	0.233	0.48	NO
72	1-20	0.864	0.48	YES
73	1-13	0.428	0.48	NO
74	1-55	0.346	0.48	NO
75	1-13	0.108	0.48	NO
76	1-24	0.679	0.48	YES
77	1-61	0.107	0.48	NO
78	1-24	0.375	0.48	NO
79	1-69	0.293	0.48	NO
80	1-22	0.218	0.48	NO
81	1-14	0.088	0.48	NO
82	1-18	0.192	0.48	NO
83	1-0	0	0.48	NO

TABLE 5

SEQ ID NO: of nucleo- tide sequence	SEQ ID NO: of peptide sequence	SEQ ID No: of contig nucleo- tide sequence	SEQ ID No: of contig peptide sequence	SEQ ID NO: in USSN 09/540,217	SEQ ID NO: of nucleotide in USSN 60/250, 583	SEQ ID NO: of peptide in USSN 60/250, 583
1	85	168	252	22974	2565	2
2	86	169	253	20878	2577	14
3	87	170	254	12791	2580	17
4	88	171	255	6072	2588	25
5	89	172	256	16749	2611	48
6	90	173	257	27958	2612	49
7	91	174	258	25431	2613	50
8	92	175	259	53	2623	60
9	93	176	260	14203	2632	69
10	94	177	261	25455	2655	92
11	95	178	262	20399	2663	100
12	96	179	263	18639	2675	112
13	97	180	264	30435	2676	113
14	98	181	265	9819	2682	119
15	99	182	266	23487	2694	131
16	100	183	267	27666	2701	138
17	101	184	268	21075	2703	140
18	102	185	269	5372	2709	146
19	103	186	270	26608	2712	149
20	104	187	271	7050	2714	151
21	105	188	272	10656	2718	155
22	106	189	273	8306	2724	161
23	107	190	274	26811	2733	170
24	108	191	275	19370	2748	185
25	109	192	276	8838	2753	190
26	110	193	277	2975	2776	213
27	111	194	278	28343	2778	215
28	112	195	279	23107	2780	217
29	113	196	280	947	2786	223
30	114	197	281	25499	2787	224
31	115	198	282	26874	2789	226
32	116	199	283	7863	2791	228
33	117	200	284	12385	2808	245
34	118	201	285	9325	2811	248
35	119	202	286	135	2830	267
36	120	203	287	948	2842	278
37	121	204	288	11131	2844	280
38	122	205	289	26590	2848	284
39	123	206	290	29769	2852	288
40	124	207	291	12703	2884	320
41	125	208	292	19931	2888	324
42	126	209	293	12950	2892	328
43	127	210	294	16635	2893	329

SEQ ID NO: of nucleo- tide sequence	SEQ ID NO: of peptide sequence	SEQ ID No: of contig nucleo- tide sequence	SEQ ID No: of contig peptide sequence	SEQ ID NO: in USSN 09/540,217	SEQ ID NO: of nucleotide in USSN 60/250, 583	SEQ ID NO: of peptide in USSN 60/250, 583
44	128	211	295	11259	2894	330
45	129	212	296	17066	2910	346
46	130	213	297	27046	2917	353
47	131	214	298	28443	2920	356
48	132	215	299	12951	2934	370
49	133	216	300	16401	2937	373
50	134	217	301	2095	2941	377
51	135	218	302	14896	2958	394
52	136	219	303	3942	2969	405
53	137	220	304	18627	2977	413
54	138	221	305	1334	2978	414
55	139	222	306	12612	2986	422
56	140	223	307	26757	2992	428
57	141	224	308	29643	3010	446
58	142	225	309	17502	3024	460
59	143	226	310	15745	3033	469
60	144	227	311	16448	3085	521
61	145	228	312	2700	3097	533
62	146	229	313	3038	3124	560
63	147	230	314	5507	3146	582
64	148	231	315	21158	3203	639
65	149	232	316	30322	3267	703
66	150	233	317	29542	3292	728
67	151	234	318	19566	3358	794
68	152	235	319	180	3399	835
69	153	236	320	2278	3404	840
70	154	237	321	6132	3542	978
71	155	238	322	138	3645	1081
72	156	239	323	29552	3652	1088
73	157	240	324	28639	3658	1094
74	158	241	325	186	3732	1168
75	159	242	326	7065	3765	1201
76	160	243	327	18073	3901	1337
77	161	244	328	513	3985	1421
78	162	245	329	6994	4036	1472
79	163	246	330	189	4080	1515
80	164	247	331	191	4260	1695
81	165	248	332	8767	4798	2226
82	166	249	333	23899	4997	2425
83	167	250	334	533	5057	2485
84		251	335	6903	2835	

TABLE 6

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
252	A	3	744	RQSSGNLTMAWTPLLLPLLTFC TVSEA SYELTQPPSVSVSPGQTATITCSGDALP KKHPYWYQQKSGQAPVLVIYEDNKR PSGIP\ERFSASSSGTMATLTISGAQVED EADYYCYSTDSSGNHRGVFGGGTRLT VLSQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKA GVETTTPGKQSNKYAASSYLSLTPE QWKSHKSYSCQVTHEGSTVEETGAPT EYLLRVY
253	B	1	1617	MEKGS GFIKYSTYKQGTIRVAEEAETA HSSVLIGPEKGVVHLATAAVLNAVWD LWAKQEGKVLAVGRELQEEKEETG WRKAQAAVEGGVGTWWLTASIRAAN AFTVRKKWGLYTYVLQILSFLQACLE VTCGHDLIMGCIKSKENKSPAICYRPE NTPEPVSTSVSHYGAEP TTVSPCPSSSA KGTAVNFSSLSMTPFGGSSGVTPFGGA SSSFSVVPSSYPAGLTGGVTIFVALYDY EARTTEDLSFKKGERFQIINNTPMVLN LGQNHPGDIWQYLETFLVVTVGVLPLS SSASTPVFDRVTNGVPTIKDLTGCCV ENRLLTSNSSDFFT LNHSNSSKTPFQN TRLVVS RGNSSSEKQFAIRFQDGKTDHA IQLSSGKKTALGREALEHPESLDSRKV GQRSRWSSQAASPISGPIQAETALLCPG DQWTQEFHTSPLLTVP HLPDIYTLDC RKDFS IYIHSFGDITQSYIFKYHLQIDDY QLCAQALKD GWTRPPPFHTAHLHFSL LTLACAETV TSAETPDALAKSRFKVK
254	A	1	717	GTRDATAEENRVLLAMVNPTVFFDIA VDGEPLGRVSFEVRGLDTKK*LLI*SIK LC*QIGGSSIFITS D*KNSCLPLIVQQCL LFLRILPLFADKVPKTAENFRALSTGE KGFGL*GVPCFHRIIPGFMCGGDCE/R HHNGTGGKSIYTEKFEDENFILKAYG VLGSLSMANA\GPNTN\GSQFFICTAKT EWLADGKPVVFGKVKEGMNIVEAME

SEQ ID NO:	Methionine	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				RFGSRNGKTSKKIISIADCGQLE
255	A	253	571	ICHQPTSLSHQ*ERNGWPGRWHSQPRS KFCRLRVLSQGDHEKKSLPSGQRP TGCASSSGSSKGLLLLPLDGLGVIVLIN PHLVVFPGMRAP*LLPRLWLRWS
256	A	1	384	VRDYNLTEEQKAIKAKYPPVNRKYEY LDHTADV/QWIVLHRA*YFFRLHAWG DTLEEAFFEQCAMAMFGYMTDTGTVEP LQTVEVETQ/GWGEEFSLSKHPQGTVEV KAITYSAMQVYNEENPEVFIIDI
257	A	675	1010	VTSSCPRKKRRFGGDRPSSSFSPPSKEL LAVKAPREGRRGPGNESRSEPSQPLDS HGPGLRRTFLPPSPRHPTKDRRTAARS GPRRKRGTNEIRGCKEEEGEKYLVA QG
258	A	5751	6430	FYFVPSQESVPSASPTGIPKHSRLKTT TEEPRGTHSQGQFTMPLAGMSLGLKS EFVPLFSATPFWVPFSSLPLFPWVLED HVCLLDCVVVDLQD\MD\FAAERHP DYSK\APEDSSGDLIFPSYFVR\QTGGSL L\TEPCRLKLQVERNLDKEISHTVPDISI HGNLSSVHCSLDLYKYKLIRGLLENNL GEPIEEFMRPYDLQRSKNSSYCPWRSV HLYVLP
259	B	144	638	MIVNLFNMFITYGDTFLPTPSSYDELY YEIIRMHQSFDNLYSMVLRRLSTNAGQ WKEAASKVTHALVNIRAINHFNPKIES YAAVNHISQLSEEQVLEVVRANYDTL TLKLQDGLDQERYSEQHKEAAFFKE LVRISITNVRRLAFHTLSQEVLLKEFS TIS
260	B	30	2477	MTPGQLSNVRAPGSAEKSGSDTG PPSAAPPGGSAGEARTAGARYLCPRSS LSGGAAATRTCGLANPEEEGPSAKCGE NGSAERTDLGGNKYNQERIQIEYVEVL FADFFREVFAICGSCDALGNWNPQNA VALLPENDTGESMLWKATIVLSRGVS VQYRYFKGYFLEPKENIHHRGDFLVT PSSSRSSFVQTGQFSGRDIDKDPKLS PVGRGWGFWEAIELCMAVKEDVRQEVG

SEQ ID NO:	Me th od	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				SHIGLLPDVAMAFVNCRGTDGGSVAVR MTRGSHSHCHLGFAYCASGFSLEPCVE NDCGASSAEVQQGFVFITSASSSSSYCT EAKRVKLTLEGLEEDDDDRVSPTVLH KMSNSLEISLISDNEFKCRHSQPECGYG LQPDRWTEYSIQTMEDPNLELIFDFEE DLSEHV VQGDALPGHVGTACLLSSTIA ESGKSAGIL TLPIMSRNSRKTIGKVRVD YIIKPLPGYSCDMKSSFSKYWKPRIPL DVGHRGAGNSTTTAQLAKVQENTIAS LRNAASHGA AFVEFDVHLSKDFVPVV YHDLTCCLTMKKKFDADPVELFEIPVK ELTFDQLQLLKLTHVTALKSKDRKESV VQEENSFSENQPFPSLKMDGMWDGNL STYFDMNLFLDIILKTVLENSGKRRIVF SSFDADICTMVRQKQNKYPILFLTQGK SEIYPELMDLRSRTTPIAMSF AQFENLL GINVHTEDLLRNPSYIQEAKAKGLVIFC WGDDTNDPENRRKLKELGVNGLIYDR IYDWMPEQPNIFQVEQLERL KQELPEL KSCLCPTVSRFVPSSLCGESDIHVDAN GIDNVENA
261	A	1	3257	MEPIEGKRSSCHKTGEATAVVHCPPG WNITMGVEASCA FVGRAGSQD TVRTG RALKALTQLRAAQGRGSQGAAA AETG LGGRRLRRAPGGGPCVGPRAAAATTL SGPRGTAQGHGGGGRSSGKG DQRAHE LAAWIPRATRARTGAAGAEPYYRA WGSGEQGRGVCRGLLR LPAGPPTPGR ARALAERLSPPRAAPRQDSWPLRGFLP PPQPLNPTSASPHPR LFSLLGARPISPW TMAATIQAMERKIESQA AHL LSLEGQT GMAEKKLADCEKTA VEFGNQLEGKW AVLG TLLQEYGLLQRRL ENVENLLHN RNFWILRLPPGSKGESPKVALGRPGVG EAAAKPVSVWFSEQVWGKLEDWQKE LCKHVMRGNC EMLVSLDYAISKSEVL SQIEQGKEPCNWRRPGPKIPDVPVDPSP APVPLPLFCSLYPPGEI HQCSVPAAKQL HV VQRTSPVTAKLSTLQPKPHFHLVLH

SEQ ID NO:	M e t h o d	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				PTPCQLLKGN TVNPTLTSTPTATACFS APLRGRAPWIYTM EGNRLNQCFQTGC WRAPGHIQAGEEAPGSRVVFTRITGSG ECRRGPEKSCGFGHSREALGEEWMIR KVKVEDEDQEAE EEEVEWPQHL SLLP\ S PFPAPDLGHLAAAYKLEPGAPGALSGL ALSGWGPMPEKPYGCGECERRFRDQL TLRLHQRLHRGEGPCACPD CGRSFTQR AHMLLHQRSRGERPFPCSECDKRFSK KAHLTRHLRTH TGERPYPCAECGRFS QKIHLGSHQKTHTGERPF PCTECEKRF RKKTHLIRHQRIHTGERPYQCAQCARS FTHKQHLVRHQ RVHQTAGPARPSPDS SASPHSTAPSPTPSFPGPKPFACSDCGL SFGWKKNLATHQCLHRS'EGRPF GCD E CALGATVDAPAAKPLASAPGGPGCGP GSDPVVPQRAPSGERSFFCPDCGRGFS HGQHLARHPRVHTGERPFACTQCDRR FGSRPNLVAHSRAHSGARPF\ACAQCG RRFSRKSHLG\RHQAVHTGSRPHACAV CARSSFSSKTNLVRHQGINHTGSRPFSC PQCGKSFSRKTHLVRHQ LIHGEAAHA A\PDAAALAAPAWSAPPEVAPPP\LFF
262	A	327	2561	ITMGSSGLGKAATLDELLCTCIEMFDD NGELDNSYLPRIVLLMHRWYLSSTELA EKLLCMYRNATGES CNEFRLKICYFM RYWILKFPAEFNLDLGLIRMTEEFREV ASQLGYEKHVSLIDISSIPS YDWMRRV TQRKKVSKKGKACLLFDHLEPIELAEH LTFLEHKSFRRI SFTDYQSYVIHGCLN NPTLERSIALFNGISKWVQLMVLSKPT PQQRAEVITKFINVAKKLLQLKNFNNL IAIVGAL\SHRSISGFKGTHS\HLSSEVT KNWNVK*QK WVSSNGNYCNYRK PFA DCDGFKIPILGVHLKDLIAVHVIFPDWT EENKVN\VKMHQLSVTLSELVSLQNA SHHLEPNMDLINLLTSLDLYHTEDDI YKLSLVLEPRNSKSQPTSPTTPNKPVVP LEWALGVMPKPDPTVINKHIRKL VESV FRNYDHDHDGYISQEDFESIAANFPFL

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				DSFCVLDKDQDGLISKDEMMAYFLRA KSQLHCQI/GAPGFIHNFQEMTYLKP/T FCEHCAGFIL/GIIKQGYKCKDCGANCH KQCKDLLVLACRR/FARAPSLSSGHGS LPGSPSLPPAQD*VFKFPGVTADNSDL DSRAITLVTGSSRK\TSVRLQRATTSQA TQT\EPVWSEAGWG\DSGSHTLPYNRY SGSLHKP/AKRHKGF AIWEK*KSPGWH \AGGDV*NPGT\EFELAPDEGEKTTQD G\EDGLTSRLAENLKANNGWLLGGGK NKKLLRKALASQEVILERTP
263	A	4463	4703	RPKMGRRSKHKPPASFOVSSLSNPGFF FFI*HCFF*LYFSYKRVNLSL*KITHYRKI LRRKTFTSETKFFPMKTEPKRVSG
264	A	1	1941	MPAPRAREQPRVPGERQPLLPRGARGP RRWRRAGAAGAVLLVEMLERAAFFGV TANLVLVLNSTNFWNWTGEQATRAALV FLGASYLLAPVGGWLADVLYLGRYRA VALSLLLYLAASGLLPATAFPDGRSSF CGEMPASPLGPACPSAGCPRSSPSPYC APVLYAGLLLLGLAASSVRSNLTSFGA D\QVMDLGRDATRRFFNWFYWSINLG AVLSLLVVAFIQQNISFLLGYSIPVGCV GLAFFIFL FATPVFITKPPMGSQVSSML KLALQNCCPQLWQRHSARSKLSQGGQ GNNGSESKLHLLVAKWQHTLGRVELT VAVFGDDYTNIVPFGISKDSARLLDKK RDRQCARVLADERSPPQPGASPQEDIAN FQVLVKILPVMVTLVPYWMVYFQMQ STYVLQGLHLHIPNIFPANPANISVALR AQGSSYTIPEAWLLANVVVLILVPL KDRLIDPLLLRCKLLPSALQKMALGMF FGFTSVIVAGVLEMERLHYIHHNETVS QQIGEVL YNAAPLSIWWQIPQYLLIGIS EIFASIPGL\EFAYSEAPRSMQGAIMG\IF FCLSGVGSLLGSSLVGTA VPLPGGWL HCPKDFGNINNCRMDLYFFLLAGIQAV TALLFVWIAGRYERASQGPASHSRFSR DRG
265	B	46	774	XACSGVPGTKCSPPSGSGYPNPYSKHV

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				LTEDIVHREVTDPDQKLLSRATLTKTNR NAHAGPERLFPANVAHSVYVLEDSIVD PQNQTLTTFNWNINPRPG
266	A	3	2523	SSLTSSMEDPAAPGTGGPPANGNGN\G GGKGKQAAPKGREAFRSQRRESEGSV DCPTLEFEYGDADGHAAELSELYSYTE NLEFTNNRRCFEEDFKTQVQGKEWLE LEEDAQKAYIMGLLDRLEVVSRRRL KAARAVLYLAQGTGECDSVDVLH WSRYNCFLLYQMGTFSTFLELLHMEID NSQACSSALRKPAVSIADSTELRVLLS VMYLMVENIRLERETDPCGWRTARET FRTELSFSMHNEEPFALLLFSMVTKFCS GLAPHFPIKKVLLLLWKVVMFTLGGFE HLQTLKVQKRAELGLPPLAEDSIQVVK SMRAASPPSYTLDLGESQLAPPSKLR GRRGSRRLTKQDSLDIYNERDLFKT EEPATEEEEEESAGDGERTLDGELDLLE QDPLVPPPPSQAPLSAERVAFPKGLPW APKVRQKDIEHFLEMSRNKFIGFTLGQ DSDLVGLPRPIHESVKTLKQHKYISIA DVQIKNEEELEKCPMSLGEEVVPETPC EILYQGMLYSLPQYMIALLKILLAAAP TSKAKTDSINILADVLPEEMPITVLQSM KLGIDVNRHKEIIVKSISTLLLLLLKHF KLNHIYQFEYVSQHLVFANCIPLLKFF NQNILSYITAKNSISVLDYPCCTIQDLPE LTTESLEAGDNSQFCWRNLFSCINLLR LLNKLTKWKHSRTMMLVVFKSAPILK RALKVQKQAMLQYVLKLLKLQTKYL GRQWRKSNMKTMSAIYQKVRHRMND DWAYGNDIDARPWDFQAEECTLRANI EAFNSRRYDRPDSEFSPVDNCLQSVL GQRLDLPEDFHYSYELWLEREVFSQPI CWEELLQNH
267	A	150	1076	PAWNARPRQVDLKLTHKKQRALLERF DIYRKVPKDLTQPTYTGAIISICCCFIL FLFLSELTGFITTEVVNELYVDDPDKDS GGKIDVSLNISLPNLHCELVGLDIQDE MGRHEVGHIDNSMKIPLNNGAGCRFE

SEQ ID NO:	Metho d	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				GQFSINKVPGNFHVSTHSATAQPQNPD MTHVIHKL SFGDTLQVQNIHGAFNAL GGADRLTSNPLASHDYILKIVPTVYED KSGKQRYSYQYTVANKEYVAYSHTG RIIPAIWFRYDLSPITVKYTERRQPLYRF ITTICAIIGGTFTVAGILDSCIFTASEAW KKIQLGKMH
268	B	264	1999	MLIYSSKTLELRETSVTPSNLWGGQGL LGVSIRFC SFDGANENVWHVLEVESNS PAALAGLRPHSDYIIGADTVMNESEDL FSLIETHEAKPLKLYVYNTDTVYTGNS TWKTCVKSSYSGALVNLNRLFSSAYT RIPCFCALRNSDKHFVNGCWLLSTYT L
269	A	67	906	NLLGGGGK KKKPPRTRGPFPGLSQPG LLWLFKRP GCSHLPSTPIKEMGLPKIH HRVGWESFSGVFLEVDFKIYKKKMNE FFSVDDNNEEEEDVEMKEDSDENGPE EKQSVEEMEEQSQDADGVNTVTVPGP ASEEAVEDCKDEDFAKDENITKGGEV TDHSVRDQDHPDGQENDSTKNEIKIET ESQSSYMETEELSSNQEDAVIVEQPEVI PLTEDQEEKEGEKAPGEDTPRMPGKSE GSSDLENTPGPDVEMNSQVDK VNDPT ESQPSCQA*RSRG
270	A	401	881	ERRERSPDQSSGRASRGPPERQSLRMS PSRAAWTSSPCRSCASQGVCAWPLNL RRIASTSWC*PMSAGIGPMAWWPSTT GPCMMSTVSTMAKPHRECPCGCFVPFA VCVVS RFPYYNSLKDCLSWHYRRPGA TLLSPSSLVTLLLVKGPGAAAADAGEI PV
271	A	184	581	ASAPVGCLTRAVCGRPPWRTNTVVEP REGTRILEFGHLKLAHVPPLEFLVNQH QPEDHVLIKRWKEEKLEPAWEGPYPV LLTTKTAVRT/DKKKKKKKKRWTHHT QVKKVPPPPESWAIVPGENPTKLKLRK M
272	A	1	3802	MRRGGWRKRAENDGWETWGGYMAA KVQKLEEQFRSDAAMQKDGTSSTIFSG

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				VAIYVNGYTDPSAEELRKLMMMLHGGQ YHVYYSRSKTTHIIATNLPNAKIKELK GEKVIRPEWIVESIKAGRLLSYIPYQLY TKQSSVQKGLSFNPVCRPEDPLPGPSNI AKQLNNRVNHIVKKIETENEVKVNGM NSWNEEDENNDFSFDLEQTSPGRKQ NGIPHRGSTAIFNGHTPSSNGALKTQD CLVPMVNSVASRLSPAFSQEEDKAEKS STDFRDCTLQQLQQSTRNTDALRNPFR TNSFSLSPHSNTKINGAHHSTVQGPSS TKSTSSVSTFSKAAPSVPSKPSDCNFIS NFYSHSRLLHHISMWKCELTEFVNTLQR QSNQIFPGREKLKKMKTGRSALVVD TGDMSVLNSPRHQSCIMHVDMDCCFFV SVGIRNRPDLKGKPVAVTSNRGTGRAP LRPGANPQLEWQYYQNKILKGKAADI PDSSLWENPDSAQANGIDSVLSRAEIA SCSYEARQLGIKNGMFFGHAKQLCPN LQAVPYDFHAYKEVAQTLYETLAS\YT HNIEAVSCDEALVDITEILAEKLTPE FANAVRMEIKDQTKCAASVGIGSNILL ARMATRKAKPDGQYHLKPEEVDDFIR GQLVTNLPGVGHSMESKLASLGIKTCG DLQYMTMAKLQKEFGPKTGQMLYRF CRGLDDRPVRTEKERKSVSAEINYGR FTQPKAEAFLLSLSEEIQRRLATGM KGKRLTLKIMVRKPGAPVETAKFGGH GICDNIARTVTLDAQTDNAKIIKAML NMFHTMKLNISDMRGVGIHVNLVPT NLNPSTCPSRPSVQSSHFPSPGYSVRDV FQVQKAKKSTEEHKEVFRAAVDLEI SSASRTCTFLPPFAHLPTSPDTNKAES SGKWNLHTPVSVQ\SRNLNLSIEVPSPS QLDQSVLEALPPDLREQVEQVCAVQQ AESHGDKK\KEPVNGCNTGILPQPVGT/ MSLLQIP\EPQESNSDAGINLIALPAFS\Q VDPEVFAALS\AELQRELKAAVDQRQR QGENSTHQQS\ASASVPKNPLNHLKAA\ VKEKKRNKKKKKTIGSPKRIQSPLNKL LNSPAKTLPGACGSPQKLIDGFLKHEG

SEQ ID NO:	Methionine	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				PPAEKPL/EKNSSGFLLSGVPGVLSSLQS DP/SLGCVRPPPPNL/AGAVEFNDVKTL LR\EWVTTISDPMEEDILQ\VVKYCTDL IEDKDLEKLDLVIKYMKRLMQQSVES VWNMAFDLFDNVQVVLQQTYGSHIK SYINITQRA
273	A	1	785	MAETEERSLDNFFAKRDKKKKKERSN RAASAAGAAGSAGGSSGAAGAAGGG AGAGTRPGDGGTASAGAAGPGAATK AVTKDEDEWKELEQKEVDYSGLRVQ AMQISSEKEEDDNEKRQDPGDNWEEG GGGGGGMEKSSGPWNKTAPVQAPPAP VIVTETPEPAMTSGVYRPPGARLTTR KTP\QGPPEIYQ*YHSSHPLAVNLPKHV ESRKDKEMEKSFEVVRHKNRGRDEV KNQALKLQLDNQYAVLENQKSSHSQ YN
274	A	463	828	HLRILRDSRTHSYFLTSLRGENNPWTD QSPCAAASRAQHLHPAAVAAATMPKT KAEGDAKGDKAKVKDEPQVTRAAIQT NTFIFKC*IEPQKQIYILYIQNSCQISLLI LPKSTLMKWMQTL
275	A	3	1901	SSVEQASVEVPDGPDLHDPDLYIEIVKN TKSVPEYSEVAYPDYFGHIPPPFKEPIL ERPYGVRQRTKIAQDIERLIHQSDIIDRV VYDLNPNYTIPEEGDILKFNSKFESGN LRRVIQIRKNEYDLILNSDINSNHYHQ WFYF\EVSGMRPGVAYRFNIIN\CEARC NRLFNYGMQPLMYSVQEALNARPWW IRMGTDIRYYINHFSRSSVAAGGA/QRG KSYYTITFTVQFST*RMDVCYFA/YIHY PYTYASTLQMHLQKLESANPQQIYFR KDVLCELTSGNSCPLVTITAMPESNYY EHICHFRNRPYVLMYARVHPG\ETNAS WGYERERWEYLHEAINPTGFRSLRRN LYY/IFKIVPMLNPDGVINGNHRCSLSG EDLNRQWQSPSPDLHPTIYHAKGLLQY LAAVKRLPLVYCDYHGHRSRKKNVFM YGCSIKETVWHTNDNATSCDVVEDTG YRTLKILSHIAPAFCMSSCSFVVEKSK

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				ESTARVVV*REIGVQRSYTMESTLCGC DQGKYKGLQIGTRELEEMGAKFCVGL L\RLKRLTSPLEY\NPALPSPALTFENDL N*IQACKVTSPYPLMSLDEDEPARFLEE VDYSAESNDELDIELAENVGDYEPSAQ EEVLSDSELSRTYLP
276	A	1076	3511	IKALSSSAEDASLVNASISSSVKATSPV KSTTSITDAKSCEGQNPPELLPKTPISPLK TGVSKPIVKSTLSQTVPSKGELSREICL QSQSKDKSTTPGGTGKPFLEFRGERC QEHSKESPARSTPHRTPIITPNTKAIQER LFKQDTSSSTTHLAQQLKQERQKELAC LRGRFDKGNIWSAEKGGNSKSKQLET KQETHCQSTPLKKHQGVSKTQSLPVT KVTENQIPAKNSSTEPKEVIREIEMSVD DDDINSSKVINDLFSDVLEEGELDMEK SQ/AGDGSSISR/TAANKRKMH*ISPQC LYLHHWHKQLV*V*CPHLDWN*KTPA EVMKVQNQENSKELVS/RAESGDSL SEDRDLLYRSQRFKETERPSIKQVIVRK EDVTSKLDEKNNAFPCQVNIKQKMQE LNNEINMQQTVIYQASQALNCCVDEE HGKGSLEEAEAERLLLIATGKRTLLIDE LNKLKNEGPQRKN*G*S/APSEFIAIPKD QFTLSEIRLP*KADFCSTVQKPDAAAN YYYLIILKSRSENMVATPLASTNSLN GDALTFTTTFTLQDVSNDFEINIEVYSL VQKKDPSGLDKKKKTSKSKKSNIHSSV MASPGGLSAVRTSNFALVGSYTLSSL VGNTKFVLDKVPFLSSLEGHIYLIKIC QVNSSVEERGFLGCPGGGRLQPKRQTI FEDVSGFGAWHRRWCVLSGNCISYWT YPDDEKRKNPIGRINLANCTSRQIEPAN REFCARRNTFELITVRPQREDDRETLV TNAGTHSVFTKNWLSADTKEERDLW MQKLNQVLCDIRLWQPDACYKPIGKP
277	B	1	2319	MQINETIWDTVGAASRHGEGERQAKS STRGCTHLAEGQGIYLQEEQSPPEMCT RVMEKREGLTIERERDPLLPVWKALGI QAHKCVAHATTNPSKATAVHPLPHLTMQ

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				PQGCLMSFFPTAAEFSTYGQELYLENN QIEEITEICFNHTRKINVIVLRYNKIEEN RIAPLAWINQENLESIDLSYNKLYHVPS YLPKSLHLVLLGNQIERIPGYVFGHM EPGLEYL YLSFNKLADDGMDRVSYFG AYHSLRELFLDHNDLKSIPPGIQEMKA LHFLRLNNNKIRGNKQEIKQTSKQASA VQSEK WVTMRAHWGLRAARRLRPP STAWNSRSPVPVEQTHCGLAVAEER KDLFMFFRSLHFFVEWFEYRKRTFKHL KWDEDYDQEPDDDYQTGFPRQNVD YGVPFHQYTLGCVSECFCTNFPSSMY CDNRKLKTIPNIPMHIQQLYLQFNEIEA VTANSFINATHLKEINLSHNKIKSOKID YGVFAKLPNLLQLHLEHNNLEEFPPFL PKSLERLLLGYNEISKLQTNAMDGLVN LTMLDLCYNYLHDSLLKDKIFAKMEK LMQLNLCSNRLESMPGLPSSLMYLSL ENNSISSIPEKYFDKLPKLHTLRMSHNK LQDIPYNIFNLPNIVELSVGHNKLKQAF YIPRNLEHL YLQNEIEKMNL TVMCPS IDPLHYHHLTYIRVDQNKLKEPISSYIFF CFPHIHTIYYGEQRSTNGQTIQLKTQVF RRFPDDDDDESEDHDDPDNAHESPEQE GAEGHFDLHYHENQE
278	A	65	262	SRRRGVSAPTSFYGRDRRMFPAQEE ADRTVFVGNLEARVREEILYELFLQVL CPREMGILSISP
279	A	1	892	MSRWGA AVGQ GALREEHFAHAHITER TRRVREGRRKRSSLLTTSPTSANAQA HFLKLKVSIDKGPQNRAGAIVPWFAK MSFPKYKPSSLRTLP\ETLDPAEYNISP ETRAQA\ERLAHR\AQL\KREYLLQYN DPNRRGLIENP\ALLRWAYARTINVYP NFKP\TPKSSLMGAFVWDFGPLIF\YYII KTERWDPNQRWLTDSRILKYEAILLER DDLTLTTDNSLNPA AFLRGPNPPEEPE HKCLDLISYQTRVRLDLSKTPFQTGRH LFIDGSSLVIGGKGHNGYSVVDGETLT K

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
280	B	1	597	MQTFTTCISYSEYSCMLLANASSHGTL YCKLRVGICLLMMPAVKNQASGSARG ATKVRRCQAGCQNEHLGELDDGTD GKNQLNIRENGGRGQNCQELESVA EKDLSQTSRDLEKMMSKHIFLKPMLSI SDLVNFLMQVSKVLVKTAEGIVLQQ PLAFPALHFHAYGNLFPVCSFKHYIYM IDHPIFISIPDFLT
281	A	1	4061	MPVPSRHINIGRSQSWDAAGWYEGPW ENAESLRPLGRRSSLTYGTAEGTWFEF NHRPQDAALPVAAEPYLYREAVYNSV AARKGSTPDFTFYDSRQAVMSGRSPLL PREYYSDPSGAARVPKEPPLYRDPGVS RPVPSYGVLSRTSWDPMQGRSPALQ DAGHLYRDPGGKMIPQGRQTQSRAAS PGRYGREQPDTRYGAEVPAYPLSQVFS DISERPIDPAPARQVAPTCLVVDPSAA APEGSTGVAPGALNRGYGPARESIPSK MAYETYEADLSTFQGGKRTVLPEFL AFLRAEGLAEATLGALLQQGFDSPAVL ATLEDADIKSVAPNLGQARVLSRLANS CRTEMQLRRQDRGGPLPRARSSSFHR SELLHGDLASLGAAAPLQTASPRAGDP ARRPSSAPSQHLETAATYSAPGVGTH APHFPSNSGYSSPTPCALTARLSPTYPL QAGVALTNPGPSNPLHPGPRTAYSTAY TVPMECLKRERNVAASPLSPHGSPPQV LRKPGAPLGPSTLPPASQSLHTPHSPYQ KVARRTGAPIIVSTMLAPEPIQFAGQA VQSDNVRKAYAAGTPVRPTSPGDTDK WGLQARAPGRAVDPRNMISAQEHKV VECMARRSATCFVFGQLCRLHSTSSDP VGVDFILSMEDVGRGKSRNPDSWSPN AVVWDASGVGGERVLQYQLDMNTVP PQGWTTTRKTRVCKHEASPSPIALAA IAKEEGVILLWTFTLGKNRLGGSATR VGYAEAQAEAPSCATTVTLSGSSHE CDSSVSSKTATCRDFMGQPWGHASIPP TPNPPPPAVVPGIFSQHENPLAFLFSRL AMKDLLPGFEPQTLDRSRASLSHVLRA

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				RPSGRVEGIRPQIMNGPLHPRPLVALL DGRDCTVEMPILKDLATVAFCDAST QEIHEKVLNEAVGAMMYHTITLTRED LEKFKALRVIVRIGSGYDNVDIKAAGE LGECEAALAAWSCPELCGPCSGGLGE AAGTGTTEQPLLA VARWLPPGRAVEH LAALPSHDTGIAVCNIPSAAVEETADST ICHILNL YRRNTWLYQALREGTRVQSV EQIREVASGAARIRGETLGLIGFGRTGQ AVAVRAKAFGFSVIFYDPYLQDGIERS LGVQRVYTLQDLLYQSDCVSLHCN LN EHNHHLINDFTIKQMRAGSIPLWNAA RGGLVDEKALAQA LKEGRIRGAALDV HESEPFSAQGPLKDAPNLICTPHTAW YSEQASLEMREAAATEIRRAITGRIPES LRNCVNKEFFVTSAPWSVIDQQAHP LNGATYRYPPGIVGVAPGGLPAAMEGI IPGGIPVTHNLPTVAHPSQAPSPNQPTK HGDNREHPNEQ
282	A	29	573	LLKISGILKTGESQNQLAVDQIAFQKK LFQTLRRHPSYPKIIIEFVSGLESYIEDE DSFRNCLLSCERLQDEEASMGASYSKS LIKLLLIDILQPAIKTLFEKLPEYFFEN KNSDEINIPRLIVSQLKWLD RVDGKD LTTKIMQLISIAPENLQHDITSLPEILGD SQHADVGKEL
283	A	927	5088	KRKRRTWKRYRSIIDHLQEKRRREVT RVDTYTLVQPEADHVESYRSMPIYPT YNEVHLDERPFLRPNIISGKYDSTAIYL DTHFRLLREEIVRPLREGILELLQSFED QGLRKRKFDDIRIYFDTRIITPMCSSGI VYKVQFDTKPLKFVRWQNSKRLLYGS LVCMSKDNFETFLFATVSNREQEDLCR GIVQLCFNEQSQQLLAEVQPSDSFLMV ETTAYFEAYRHVLEGLQEVQEEDVPF QRNIVECNSHVKEPRYLLMGGRYDFT PLIENPSATGEFLRNVEGLRHPRINVLD PGQWPSKEALKLDDSQMEALQFALTR ELAIQGPFGTKTYVGLKIVQALLTN ESVWQISLQKFPILVVCYTNHALDQFL

SEQ ID NO:	M e t h o d	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				GRHLQLSGRPGIVRVGWKGATVEIPEG SFTLRELNRNREFRRNLPMHLRRAYM SIMTQMKESQELHEGAKTLECTMRG VLREQYLQKYISPPALGKSHEWPQCRI VNGFSSQHWKSHDAGVA*VLVSLS RKVFLQQLRIQPQAEGDEEEEGEE/RE FRLIRDSQREADPDFKQTG*LRRKRW* GPSGGRKRVEQTRSWLKCFWP*G*TI VALGQQLDRSKPQESGRPS/DNQKKK MKKRVKDELRLNTMTAAEANEIEDV WQLDLSSRWQLYRLWLQLYQADTRR KILSYERQYRTSAERMAELRLQEDLHI LKDAQVVGMTTGAACKYRQILQKVEP RIVIVEEAAEVLEAHTIATLSKACQHLL LIGDHQQLRPSANVYDLAKNFNLEVSL FERLVKVNIPFVRLNYQHRMCPEIARL LTPHIYQDLENHPSVLKYEKIKGVSSN LFFVEHNFPEQESKRRKSHQNQHEAH NVVELCKYFLCQEYLPSQITILTTYTGQ LFCLRLMPAKTFAGVRVHVVDKYQ GEENDIILLSLVRSNQEGKVGFLQISNR ICVALSRAKKGMYCIGNMQMLAKVPL WSKIIHTLRENNQIGPMLRLCCQNHPE THTLVSKASDFQKVPEGGCSLPCEFR GCGHVCTRACHPYDSSHKEFQCMKPC QKVICQEGHRCPLVCFQECQPCQVKVP KTIPRCGHEQMVPSCVPESDFCCQEP SKSLRCGHRCSHPCGEDCVQLCSEMV TIKLCGHSQPVKCGHVEGLLYGGLL VKCTTKCGTILDCGHPCPGSCHSCFEG RFHERCQQPCKRLICSHKCAQKPCIGE CPPCQRTCQNRCVHSQCKKKCEELCSP CVEPMC SRCQHYQCTKLCSEPCNRPPC YVPCTKLLVCGHPCIGLCGEPCPKKCR ICHMDEV TQIFFGFEDEPDARFVQLED CSHVFVQALDRYMNEQKDDEVAIRL KVCPIQVPIRKNLSYGTSIKQRLEEIEII EEKYPGLIRGNQNPQGTAA
284	A	381	2040	AERKLSEKSLVVAAPDNRNPAFTT MGWLFLLKVLVLAGVSFSGFLYPLVDFCI

SEQ ID NO:	Methionine	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				SGKTRGQKPNFVILADDMGWGDLGANWAETKDTANLDKMASEGMRFVDFHAAASTCSPSRASLLTGRGLRNGVTRNFAVTSVGGGLPLNETTLAEVLQQAGYVTGIIGKWHLGHHGSYHPNFRGFDYYFGIPYSHDMGCTDTPGYNHPPCPACPQGDGPSRNLQRDCYTDVALPLYENLNIVEQPVNLSSLAQKYAEKATQFIQRASTSGRPFLLYVALAHMHVPLPVTQLPAAPRG/RKSLYGAGLWEMDSL VGQIKDKVDHTVKENTFLWFTGDNGPWAQKCELAGSVGPFTGFWQTRQGGSPAKQTTWEGGHRVPALAYWPGRVPVNVSTALLSVL\DIFPTVVALAQASLPQGRRFDGVDVSEVLFGRSQPG\HRVLF\HPNSGAAGDFGALQTVRLERYKAFYITGGARACDGSTGPELQHKFPLIFNLEDDTAEAVPLERGGAEYQAVLPEVRKVLADVLQDIANDNISSPDYTQDPSVTPCCNPYQIACRCQA A
285	A	1	885	PVATTISQPLSLEADMWSIGVITYILLSGASPFLGDTKQETLANITAVSYDFDEEFFS\ETSELAQDFIRKLLG*ETRKRVTIQEALRHPWITSKGEGRAPEQRKTEPTQLKTKHLREYTLKCHSSMPPNNCYVNFERFACVVEDVARVDLGCRAVEAHDTIQDDVEALVSIFNEKEAWYRDENESARHDLSQLRYEFRKVESLKKLLREDIQATGCSLGSMARKLDHLQAQFEILRQELSDLQWIQELVGSFQLESGSSEGLGSTFYQDTSESLSELLSRSCTEEFLAGWKL
286	C	187	342	MVPVFSVEKDGEELGSFRPRWADWLTGLLEWVSVESLSIYCISQPVYMWVE
287	C	188	207	MWHLSV
288	A	153	503	HPHSPDPGSALGSSSGGWLPAPLSPCRG*AGAGGGRRRCRGPWSRAG*ACSGHAGSRCCPA*SVCGGLPGGAPGCLCKGGSAGFCCQGPCSCSGCSGSGHGGYRHRQGRPLSASQ
289	A	1	4964	SVYKADLEWLRGIGWMPEGSVEMNR

SEQ ID NO:	M e t h o d	Predicted beginning nucleotide location corres- ponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corres- ponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion
				VKVAQDLVNERLYRTRPEALSFTSIVD TPEVVLAKANSLQISEKLYQEAWNKD KSNITIPSDTPEMLQAHINALQISNKLY QKDWNDDTKQKGYDIRADAIEIKHAKA SREIASEYKYKEGYRKQLGHHMGFRT LQDDPKSVWAIHAAKIQSDREYKKAY EKSKGIHNTPLDMMSIVQAKKCQVLV SDIDYRNYLHQWTCLPDQNDVIQAKK AYDLQSDPLYRNAWEKEKANVNVPA DTPLMLQSKINALQISNKRYQQAWE VKMTGYDLRADAIGIQHAKASRDIA DYLKTAYEKQKGHYIGCRSAKEDPK LVWAANVLKMQNDRLYKKAYNHDK AKISIPVDMVSISAAKEGQALASDV RHYLHHWSCFPDQNDVIQARKAYDLQ SDTEPCSLAQAGVQWVADMTARGQSP LAPLLETLEDPSASHGGQTDAYLTLTS RMTGEEGKEVITEIEKKLPRLYKVLKV SSIIDSLEILFNKGETHSAVVDFEALNVI VRLIEQAPIQMGEAAVRWAKLVIPLVV HSAQKVHLRGATALEMGMPLLLQKQ QEIASITEQLMTTTLHRSGSFINSLLQLE ELGFRSGAPMIKKIAFIWKSIDNFAL NPDILCSAKRLKLLMQPLSSIHVRTETL ALTKLEVWWYLLMRLGPHLPANFEQ VCVPLIQSTISIDSNASPGNSCHVATS PGLNPMTPVHKGASSPYGAPGTPRNM LSSNLGGMATIPSIQLLGLEMLLHFLLG PEALSFAKQNKLVLSLEPLEHPLISSPSF FSKHANTLITAVHDSFVAVGKDAPGN KKEKPGSEVLTLLKSLSEIVKSEVFPV SKTLGTPALFLIQLIFNNFLECGVSDER FFLSLESLVGCVLSGPTSPLAFSDSVLN VINQNAKQLENKEHLWKMWSVIVTPL TELINQTNEVNQGDALHNFSAIYGAL TLPVNHIFSEQRFPVATMKTLLRTWSE LYRAFARCAALVATAEENLCCEELSSK IMSSLEDEGFSNLLFVDRIIYITVMVDC IDFSPYNIKYQPKVKSPQRPSDWSKKK NEPLGKLTSLFKLIVKVIYSFHTLSFKE

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				AHSDTLFTIGNSITGHISSVLGHISLPSMI RKIFATLTRPLALFYENSKLDEVPKVY SCLNNKLEKLLGEIIACLOFSYTGTYDS ELLEQLSPLLCIIFLHKNKQIRKQSAQF WNATFAKVMMLVYPEELKPVLQTQAK QKFLLLLPGETVEMMEESSGPYSDGL KLESSSLKVKG EILLEEKSTDFVFIPPE GKDAKERILTDHQKEVLKTKRFEEQM DSDIVIPQDVTEDCGMAEHLEKSSLSN NECGSLDKTSPEMSNSNNDERKKALIS SRKTSTECASSTENSFVVSSSVSNTTV AGTPPYPTSRRTFTITLEKFDGSENRPF SPSPLNNISSTVTVKNNQETMIKTDPLP KAKQREGTFKSDSEKIVNGTKRSSRR AGKAEQTGNKRKPLMRSEPEKNTTE SVEGIVVLENNPPGLLNQTECVSDNQV HLSESTMEHDNTKLKAATVENAVLLE TNTVEEKNVEINLESKENTPPVVISADQ MVNEDSQVQITPNQKTLRRSSRRR/YR SSRVYH*KPR*GK*SSKKGTT*GRRKTS SEESIA YKR
290	A	2310	2635	KDAYMFKKGLLALALVFSMPVFAAEH WIDVRVPEQYQQEHVQGA INPLKEVK ERIAVAPDKNDTVKVYCNAGRQSGQ AKEILSEMGYTHVENAGGLKDIAMPK VKG
291	A	2	359	SSPSCHLVKKIKIKMKSPALRGLSRQH TKSPVTFWWMTFGDTSRPSQDTLPMD LQQLLGVTKVCSKATSPTSQRGQEVIS TPTSKSGPFIGRGS*G*SGRWERPSCCL HFSYPQLRGLC
292	A	834	1913	REPAGAGAYMRACARVRRRGDRRPR RSPRPRDPAVRARARSAPPPLFIAAAG GGSGWRLYADSGEEYGIMAFALFVL LGFALLGTHGA\SGAAGTVFTTVEDL\ GSKILLTC\SLNDSATEVTGHR\WLGK GVVLKE\DALPGQKT\ESFKVDSDDHV GMKYS\CVFLP\EPHGHGPTIQASTGPP RVEGL*SSFRTHSTRGKTGLVGSCK\SE FVPP\VTDW/APWYKITDSEPQGPSLNA

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				QRTRFF\VGPSAGPVKSYQH*EPEHIGP PPARNRCNGTSSKGLRPRPLQFLRVRT AT*AAL\WPFLGIVG\EVLVL\VTNFIYE KRRK\PEDVL\DDDDAGSAPLKE/SAGQ HQN\DKGKKRSARGNFS
293	A	1	936	MKVLLSVKERAEEEEKLAAHLRSFA AKKAKKYDSVKKEKTLQDVDLTQHQ HKQTRALSGGLKRKLSLGIAFMGMSR TVVLDEPTSGVDPCSRHSLWDILLKYR EGRTIIFTTHHLDEAEALSDRVAVLQH GRLRCCGPPFCLKEAYGQGLRLTLTRQ PSVLEAHDLDKMACVTSLIKIYIPQAF LDSSGSELYTIPKDTDKACLKGLFQA LDENLHQLHLTGYGISDTTLEEAEGRT AAPEPPMLEDGHA\VTQRF\SFQVVGCE DDRTTWVQAQGASAPGGQRPQEDLPS FPQDGRSRAQFKDPHQFSN
294	A	1	1743	MASHAYDKNQANANVLVHLCFYNRIPK TGAYYLD\SRVSISYLIGHHIDMGLET ATSKNEFIFDSASTLLGMLFRKPSQHSL SLFSKKFQENLIYLESDDCLPPPPPPW SEPPSFLTWTIVTVFQWVSLLSLPNIQ VILYRAVG\VVPSQPKSDNLKGWGR VVKEKLRSEIPDWKIKSIHILERTASSST EPSVSRQ\LEPEPVPLSKEADSWEIIEG LKIGQTNVQKPKDHEGFMLKKRKWPL KGWHKIQKGKVHGSIDVGLSVMSIKK KARRIDLDTEEHYHLKVSVFNSFS IRGNDLPTPVVKSQDWFD\WVSKLRH HRLYRQNEIVRSR\PDASFHIFPSTSTAE SSPAANVSVM\DGKMQPNSFPWQSP CSNSLPATCTTGQSKVAAWLQDSEEM DRCAEDLAHCQSNLVELSKLLQNLEIL QRTQSAPNFTDMQANCVDISKDKRV TRRWRTKSVSKDTKIQLQVPFSATMSP VRLHSSNP\NLCADIEFQTPPSHLTDPLE SSTDYTKLQEEFCLIAQKGKGASKKQA KRNAAEKFLAKFSNISPENHISLVSNVD SYDVNVIKHFLQ
295	A	1	1248	MLRTRKAPH\SWVKSSSNTVHYRVSVV

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				CLHDHVTDWEWQLTATARHPKRVSH YILWDQEKTKIKIRKDIIRILPSLDVEVK DITDSYDANWFLQLLSTEDLFEMTSKE FPIVTEVIEAPEGNHLPQSILQPGKTIVI HKKYQASRILASEIRSNFPKRHFLIPTS YKGFKRRPREFPTAYDLEIAKSEKEP LHVVATKAFHSPHDKLSSVSVGDQFL VHQSETTEVLCEGIKKVVNLACEKIL KKS YEAAALLPLYMEGGFVEVIHDKKQ YPISELCKQFRLPFNVKVSVRDLSIEED VLAATPGLQLEEDITDSYLLISDFANPT ECWEIPVGRNLNMTVQLVSNFSRDAEPF LVRTLVEEITEEQYYMMRRYESSASHP PPRPPKHPSVEETKLTLTLAEERTVDL PKSPKRRR
296	A	1	906	MFAFEPLGGCRPWRLSLPGLGSRLFRT YGAADGRRQRRPGREAAQWFPPQDR RRFFNSSGSSDARMGDPSQSDDPDDPD DPDFPGSPVRRRRRCPGGRVPKDRPSL TVTPKRWKLRARPSLTVTPRRLGLRAR PPQKCSTPCGPLRLPPFSPRDSGRLSPD LSVCGQPRDGDELGISASLFSSLASPCP GSPTPRDSVISIGTSACLVAASAVPSGL HLPEVSLDRASLPCSQEEATGGAKDTR MGSVRVLRDPVGVNLYEHSVSKCHVG QPDTPREKVKAAPPEELCLHALQHPRS EQADC
297	A	574	869	QGAFWLLFSSPRSFFLLSVP/WWLPES RWLLHGHKSQLA VQNLQKVAHRGDW PGSGHPAPQSQHSSLRRSAARSRPPCW ARRWRAPPHTPRVAGGSGC
298	A	225	749	ESVTFEDVAVEFIQEWALLDSARRSLC KYRMLDQCRTLASRGTPPCKPSCVSQL GQRAEPKATERGILRATCVAWESQLK PEELPSMQDLLEEASSRDMQMGPGLFL RMQLVPSIEERETPLTREDRPAQDPP WSLGCTGLKAAMQIQRVVIPVPTLGH RNPWVARDSGAIGNG
299	A	1	591	PLPLDQRLLASITPSPSGQSIIRTQPGAG VHPKADGALKGEAEQSAGHPSEHLFIC

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				EECGRCKCVPCTAARPLPSCWLCNQR CLCSAESLLDYGTCLCCVKGLFYHCST DDEDNCADEPCSCGPSSCFVRWAAMS LISLFLPCLCCYLPTRGCLHLCQQGYDS LRRPGCRCKRHTNTVCRKISSGSAPFP KAQEKSV
300	A	1	1569	MKTCLAFPLAFHHDSNGSAVLRLOAT HGISSDSPLPSVEKASHSPDPSEYFRKH PPVRRSGLRTKRTSPGPGARVPGSQSF RSAEACGVAALECWRRRVVPVPLSSPA EVQVLLKKALRPESRPFRNQILHNCER NWGNKGWKGLVGRSESQTGQSEKLS MSSHHRGTVREELVVEEYIGGWCLCG SAWKLLVTGLEQLFSRTRPQEEAVD KTWRTARQLESGTLLCRHCITLPWPSE RNGGCFLSPSNMLVCELRLSVIVASP EPSTEHTQEHLSGDEFKESQPSRKEKSL GLLCHKFLARYPNYPNPVAVNNDICLDE VAEELNVERRRIYDIVNVLESLHMSR LAKNRYTWHGRHNLNKTGLTKSIGE ENKYAEQIMMIKKKEYEQEFDIKSYT SVNSRKDKSLRVMSQKFVMLFLVSTP QIVSLEVA AKILIGEDHVEDLDKSKFKT GSLVRLFAPCLSGAGSKLPGLVEALAF EVSLAAFSVVASVESFEPVALEEWWVH TVGLRPWGGVTLWWA
301	C	236	481	MDLIVYHKKSDISNQPSIPTCALFFPCV SLEPFQLFPVKQTARRPPPYSSPGKSTG NVIPFGHGFPTLQPKXQITPVGGQY
302	A	1	1755	MRQTKTEYIQEFNQEATVARALEGQE KPTGPRNTCLGSNNMYDIFNLNDKA LCFTKCRQSGSDSCNVENLQRYWLNY EAHLMKEGLTQKVNTPLKALVQNLS TNTAEDFYFSLEPSQVPRQVMKDEDKP PDRVRLPKSLFRSLPGNRSVVRLAVTIL DIGPGTLFKGPRLGLGDGSGVLNNRLV GLSVGQMHVTKLAEPLEIVFSHQRP NMTLTCVFDVTKALVGGYDILAIYE VEHFQQEQCVAVISVCSRGGKGSAC GHWGKGLTTEHSSPVPVAVTHLSLARIA

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				EKGKAGCPARACRVHSWVLVLSGKRE VPENFFIDPFTGHSYSTQDEHFLGIESL WNHKNYWINMQDCWNCKVPREGEL GDPEERLAHL/SWWLGLSVHLHGGRS QSAAPELPSHHPVPAALMVYEPLPATT GLDL*PG*PCEMGVHAPGD**VSAVLD *RRRQWDKR*G*CGKSGQGG*G*ELR HAPLVVEQIEISPEGTNILEIKEWYQNR EDMLELKHINKTTDLKTDYFKPGHPQ ALRVHSYKSMQPEMDRVIEFYETARV DGLMKREETPRTMTEYYQGRPDFLSY RHA
303	A	3	1376	GDQKVHPFSTPSPGTPAFHIPTTFSPAA GPGHHLPMDPGEGLAEGPGLP/GSSG* RPL*VPSRRASHCP\PGATKARGGRCR GPAATTG*AACAGRTAAPG*PGASPPA AQALHHSLLQEPGEHRGRPGPSASAPSA GTVDQVGGGAERMPTTPGPRHAVGEC GPTCSASLRGPL*PLPNLAAPAQWGS QLQGEEQIQVPSCCFAPGIQRLLPRPQT QEPGF*TQTPDPGLKPQDSKPRLPGLQ TQTPDPGPRTRADGFPDQRGPV\GQQQ WEGAPGGHTLGNSGGSCLA/GPPW*RS EGHEECSSCQSQFGELRLWLPRGGW AEGVSAGSHGPPWPAGPAPPGPQPLG WDAGPHFPEESRTRPGPDPEP*KDHGT VL*LTQRKHRDGHKEPRTKIQLPVPGA EGQTCPEPWAGAHRRNANWQAQGS RRERPSGFQTPRSHWVPSAGRSGLGP QFSL
304	C	215	343	MSGRVFRCQALVAYTVLSELFTEAKE QRLATDEGQKEFSAES
305	C	215	339	MSGRVFRCQALVAYTVLSELFTEAKE QRLATDEGQKEFSAE
306	A	2	2483	GKYYKLSSGTAPTCVSLGWGLARGDS AAPALGSRTSACAPCSHG TWKLSLEPS DRLSPCDRSSEEAHTHAPHRLALVAS LPWSRLPLLAPQSHSEAEATSQPTGVE NHHQKTRYVKAGGPVICRSLPESRGFL WASEGRKCMLIGSWAAMGRLRKSTIS

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				SRFGPQTLAGTGRPQAIPVLKKHSDAV LLGVCFLKLLHQHHQELGENADSQTL PQTHWEFILSEDYNKMTPVKNYQVLE VLARAMRQEKQIKSIQLGKEEVKLSVF ADDMIVYLENPIVSAQNLLKLISNFSK VSGYKINVQKSQAFLYTNNRQTESQIIS ELPFTIPSKRIKYLGIQLTRDVKDLFKE NYKPLLNEIKEDTNKWNIPCSWVGRI NIMKMAILPRVIYIFNAISIKLPMTFFTE LEKTTLKFIWNQKRARIAKTILSQKNK AGGITLPDFKLYYKATVTKTAWYWY QNRGVDQWNRIEPSEIIPHIHNLIFDK PDKNKKWGKDSLFTKWCWENWLAIC RKLKLDPFLTPYTKINSTWIKDLNVRP KTIKTLEENLGITIQDIGMGKDFMSKTP KAMATKAKIDKWDLIKLSFCTAKET TIRVNRQPTWEKIFTIYPSDKGLPRIY KELKQNLQEKIKQPHQKVGKGYKQTF LKRRHLCSQQTHEKMFIITGHQRNAKQ NHNKIHLTPVRMAIHKKSGNNRDMDE AGNHHSEQTIARTENQAPYLLTHRWE LNNENTWTQVEEHHTLGPIVGVICRKV FPGNSGPSKPSGLHFSQPLPQVTSVVA KITIVPWEMKLIAMGVQDELNIAFHKN HLLMNDTTIHMTPIYIQPAPKS
307	A	1532	1937	TPLPVCHFTCRKNHLKGMENLCLHKK CMWMSTVAFSIIAKTWKQPRCPSAAPS WKQPTHLLTTGDWANGLG*FSTREYVT A*ERTNQSKPDTTTWVNLTDVQLSNSS QAPRGVSTTLQFPVLGTVDKSGVTMT FWV
308	A	1	939	MGNKTYGGQNQMLIFAFTLHSLFLNS GDGRLSFESSQKPGGFNIAIQTSPSL RKHFVPVFKRKRLTASKSVEEMPTASQS AIHVNGNLSEQDIVSSDLAYLRLAQLH EDGPRRVKVSHAFLPRVPKVQSNGPVS ICLEAGTWSLEKATAAIQVPDDIYHS PSWEARESALSPDRSAEHNSLSRPSDP GLSLQPQLLPTLCLPFHVL YTRSPQSLG HGPIAVHGLLGTMLRSRRTWSFLYPGF

SEQ ID NO:	Methionine	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				LPWCSEGRIGSRVGLENECKVSLSGSSS QPMGEPEGRWSSPEVGPLASPGSPLIA WAKLRFVPPVDDLDPV
309	A	1	1528	MDSQEVEKYPNTSVACEEIPFSGIHVA GGKSGALEHGKDDLDEPIENPLFCFSSF SNALAILLPKVFLKNIHILQFIYRSFHL TMAKAKFEGAESVEPVSPSQPKRPSYV PLEELWTRLTKGNSRPQQRDREKGGW MKGVQQGHQGVGKQEEGSENIKEKA GIVVCEVPNNKLDKFMGILSWKDSKH SLNNEKIILRGCILRNTSWCFGMVIFAG PDTKLMQNSGKTKFKRTSIDRLMNTL VLWIMLISQPVVEFIMRGHSYFINWDR KMYYSRKAIPAVARTTTLNEELGQIEY IFSDKTGTLTQNIMTFKRCRINGRIYGE VHDDLQKTEITQLIHRWLARLKKKK REKNQTDTIKNDKGNITDLAETQTTI REYYKHL YTNKLENLEEMDKFLDAYT LSRLNQEEVESLSRPITSSEIEAVINSLP TKKSPGPDRFTAELYQKYKEELEKEPV DFSVKSQADREFQFFDHNLMESIKMG DPKVHEFLRLALCHTMSEENSA
310	A	104	315	DWTVGFVGNSTELPGSVGRRSLWES SYSTRTRNQGRQAIQIHS*LREVERKS GQKATMSSGGGYCQPE
311	A	271	1020	AIRQEKEIKGIQLGKEEVKLSLFADDMI LYLENPIVSAQNLLKLISNFSKVSGYKI NVQKSQAFLYTNNRQTESQIMSELPFTI ASKRIKYLGIQLTRDVKDLFKENYKLL LKEIKEDRNKWKNIPCSWVGRINMVK MAILPKVIYGFNAIPIKLPMIFFTELEKT TSKFIWNQKRAHIAKSILSQKNKAGGI TPPDFKLYYKATVTKTAWTRKIYSK KRKVKISVEPVYSGVTLTTAIQLVPLLC TAL
312	B	1	889	MDYEKADKRPTPWEAAAKSPLGLVD DAFQPKNIQESIVANVVSAARRKVLPG PPEDWNERLSYIPQTQKAYMGSCGRQ EYNVTANNMSTTSQYGSQLPYAYYR QASRNDSAIMSMETRHL YTRQLYCYS

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				FGDSGNFCENTNGRPAADAVRGLTILS LSTTSIPSSGISEALISENENKNLEHLTH GGYVESTTLQIRPATKTQCTEFLAPV KTEVPLAENQRSGPDCAGSLKEETGPS YQRAPQMPDSQRGRVAEELILREKVE ASTQNNYYVGELTGVTLQNGYGEKPI LATQX
313	B	471	1448	MLKYTGAHQEVELSAPIVTKMATQYL RENLFGRFDNDNFCLLNGDAVIFRMV VSWKLVEKERTEIMLKYTGAHQETWL KDLEESPLYEALSMRGQDKETLGLWI QLPWCPWGKAVQMHHMNPSSFQLDTK PGKGELAGRLIIPHQEASILELSLLMT CCVEREGKTSVRVAAGECTASETPN QGAGRLSLWQQLTSKKEIMEKEHTD CVSQTVALISTCVKEGGSRPADKDL GGGLEAESPKQSPNLCVILRHNLASRP GQLALVTVGTMQGRPLSHSSEVKGTT FVTHSVAPAGKEKDEERGIGDLEHARDL RNSPTPLFY
314	A	1	903	MSELPFTIASKRIKYLGIQLTRDVKDFF KENYKPLLNEIKEETNKWKNIPCSWV GRINIVKMAILPQRLPHGFLPNMKLEV VDKRNPRILRVATIVDQVDDQVRKHSM TASSGSGVSADLNTASQPLWLLKTAL AVSSSVKVHPPVSGLIFSSRTLSSFMG IMREDLGFSRRQILHFPMALESKSAGRR SKIGQLDALSDQDFGLRDRDSSKKGTY PNPENFSWTEYLEATQTNAVPAKVFK MDSDVGENRKILRDERPNYSQYTPFSR CDNASYKENVFLQKLERNTPDIAERFD CLLLTY
315	A	12	253	MMSWSSAEKGPEGHRRREWPSQWED EP*NQNGESRKKERKEKRRKET*EERR GEKREKREKKRRREGMSISFARRYSI L
316	A	2020	3942	SQRTAGNPCLHPVSLCGSASWMPMIM PQRWSSLCSAMEKPASPCL*MPPQATC WCPSRLPMAWASGH*HTSTGHSQLP IPFDNHCGKRCRLGGKWRAPLQHPQW

SEQ ID NO:	Methionine	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				K
317	A	2	271	RRPTRPQEEGGSESSTMTELETAMGLI DVFSRYSGSEGSTQTLTKGELKVLMEK ELPGFLQLSGPGLGHQHTLLLLFRSAS WSRLVPQ
318	A	1	455	MVEGKEEQVTSYVDVQRACAGIRGAF EKPQGAVARVHIGQVIMSICTKLQNKE HVIEALCKANFKFPGRQNIHFSEK WDF TKFSVDEFEDMMAEKQLIP/DNCGVKY TPNRDPPDKRDGVALQHGLLLWQLLQ NKIRLHQGREKKPPKKARR
319	B	1	370	MSRRKQGKQPQLSKREFSPRDREEVTT CFPCPPPTPPGLVTSPAPRARLGQPCS ARNENLLEADYDPPEPIVLRNTTATHT HSHSVSPSLYNSDSPQPLKHLGAVSAA ETGVRGMMGMYLKPX
320	B	1	3204	MCELDILHDSLYQFCPELHLKRLNSLT LACHALLDCKTLTLTELGRNLPTKART KHNIKRIDRLGGRHLHKERLAVYRW HASFICSGNTMPIVLVDWSDIREQKRL MVLRASVALHGRSVTLYEKAFPLSEQ CSKKAHDQFLADLASILPSNTTPLIVSD AGFKVPWYKSVEKLGWYWSRVRGK VQYADLGAENWKPISNLHDMSSSHSK TLGYKRLTKSNPISCOILLYKSRSGRGR NQRSTRTHCHHPSPKIYSASAKEPWIL ATNLPVEIRTPKQLVNIYSKRMQIEETF RDLKSPAYGLGLRHSRTSSSERFDIML LIALMLQLTCWLAGVHAQKQGWDKH FQANTVRNRNLKIYSHMVTWGNIEG ISQTQAFAKENNQKAYKETYGVSHTIR HDMQLQPKQQQNEKYQVPQFDQSTIK NIESAKGLDVWDSWPLQNADGTVAEY NGYHVVFALAGSPKDADDTSIYMFYQ KVGDNISDSWKNAGR VFKDSKFDAN DPILKDQTQEWSGSATFTSDGKIRLFY TDYSGKHYGKQSLTTAQA YRLEIVSL EMQKNGAADAAPYRQIEYWALGHGD DIKKA VAFWSSGWPVGFSKMEKAGKI LRSQVKFPEYMEESSCLGRGSLMSLNN

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				TSSSNGSFIFVLPLKLLRVGDTYNSSDQSRMAWRLTIEFGGSELHLGVREEAGHQKGLVHESGNPARSSGSDPQHARHRQPSATRAAAAAAAAAAALPAPLSLPVPTSAIQVRVTAYPLLAQCLQAAPPLLGS GCGQEGTGAGGGGGAAGVREQLDR RAAAE PGDLP GGKRV RGRGAREGPGV GAEGPPLERNRPSSPLPWLAAPAAGAS QFAEIQQAGKGEMRAKDAERGRAKLR GELSSSGRKIFDPDDL YSGVNF SKVLST LLAVNKATEDQLSERPCGRSSSLSAAN TSQTNPQGAVSSTVSGLQRQSKTVEM TENGSHQLIVKARFNFKQTNEDELSVC KGDIIYVTRVEEGGWEGTLNGRTGW FPSNYVREIKSSERPLSPKAVKGFETAP LTKNYYTVMSRSLTSTVLKNSKVARIH SKPY
321	A	724	1296	RSPTLSSPPPAASKAQAALALRSEAQAQM PRLPAPRVRSSAAASAAARSLAETFS GKECQWTDACLSHPCANGSTCTTVAN QFSCCKLTGFTGQKCETDVNECDIPGH CQHGGTCLNLP GSYQCQCLQGFTGQY CDSL YVPCAPSPCVNGGTCRQTGDFTF ECNCLPETVRRGT EL WERDREVWNGK EPDEN
322	C	150	362	MPGPAAASHRASTYVSTWSCP PHHSW HAWQCTVARPHLQTSHCCTSG LPLAD MESRLVASPSEWNKLTWAQ
323	A	1133	1350	ESQSLETGLRALIWSTRKPGGPVLGGL VLIKWAWASRSPASPSDPSPGNLCCS PTSPATKPRVDGPFVIRN
324	A	1	615	MNWVLQKFITAWKFMGYRKSSNSAR GSTIKEHIELD AQRPVRRSGPIQASGAH PKKGRGVSCSVEEPSDQQSPSPSPLTF QPKDGEINFSVIGQYVDYL VKEQGVK NIFGKSTLGMSLVSSSVFRRYILPGYQ PRGHTVMVSQVNIDFQTREATRKNLQ EPSLTCFDQAQGVHSLMEKDSYPRFL RSKMYLDLLSQSQRRLS
325	B	1	669	MVMSFVKPGVKEKEQVKKRDGEFNSE

SEQ ID NO:	Metho	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				HAELDVPARDTKRKFWEPTRLSSTLRT SSDPLFSVPISITMVCEPGSKSLQSCCLT AGGANVWEKSTCRKKSRLVLRNVK VPGKSPCGELLPIKKNQNLNILLQPV TETLEGPPGLGLDAEGPEKRHSWILLP CPGIDHTSGLEVMSDLYHRKGNSLHPQ GKRTKDARKESFPQKMGQFPLQSLAVI YPEAGT
326	B	1	2043	MEEHSMMLMGRKNQYRENGRIAQELEK TTLKFIWNQKRACITKSNLSQKNKAGG ITLPDFKLYYKATVTKTAWYWYQNRD IDQWNRTEPSEIMPHIYNLYLFDKPEKN KQWGKDSL FNKRFWENWLAIFRKLKL DPFLTPYTKINSRWIKDLHVRPKTIKTL EENPGITIQDTGMGKDFTSKTPKAMAT KAKIDKWDLIKLSFCTAKETTIRVNR QPTKWEKIFATYSSDKGLTSRIYNELK QIHKKKTNNPIRKWAKDMNRHFSKED IYAAKKHMKKCSPSLAIREMQIKTTMR YHLTSVRMAIIQKSGNNRVLPLAPLAL AALWMDPVMGMDGLLGDSSEFQGL SATFFASVFHSALHIDSAPGPCIGPGDS SADSSPTFLPPEAKRKNYLLWRKNLK KFSDDPKRLIEGFPKLALTFRLIWKDIN VLLGQALLQEERQTICGAAIHCRNDLH LENANYPGGATAVPQLDPNQDYNK AGIWARNHRLLCLIETTTQQPTNAHSP QTQRQQHDTDKPQPNPPAKTTGVPVS FLAFLYQYLCGHISISWPVVILKYAASV YGISLADRKRQYDRYFRYERLRTIKPN FLPFQIFKSGSVVCLKAGFTIGKVHNT VTALKVSDTRRAQHLQTGCWSAVVT HPNNLENVVRHPPEALAASYNKPFICS LVTLQGAFVT
327	A	1	1113	MLMVYPRTNKQNQKKKWKVEPPTPQ EPGPAKVAVTTSSSSSSSIPSAEKVPTT KSTLWQEEMRTKDQPDGSSLSPAQSPS QSQPPAASSLREPGLESKEEESAMSSD RMDCGRIPSTPNHRRSQVIEKFEALDIE KAEHMETNAVGPSPSSDTRQGRSEKR

SEQ ID NO:	M e t h o d	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				AFPSKQDFTNEAPPQAPLPDASASPVST PKSQVTGQEGQNISWDMAVVLKATQE APAASTLGSYSLPGTLAKSEILETHGT MNFLDSSPQVRYHPRNLGTACNQAGL DRYYPEGPLPRSGDDTVLSRPAWSKL AATRSQRLDPRQRGSTEREKGEAHND PLAAAPISAAGSRRGALASWLASPTRS QNPAPPTPDCRAPLTESARPTS
328	C	1	354	MGKWDGGFNFMVFCVLENTCSLNRSL LENLIFATLKISWGGAGIKGWNHMK QLLTCVVFDAQFQLSPQGSLEQKHLIL YPELTGPIELDPICYHHLSNLLSQTPK ASFEVLHQNH
329	A	1	768	PIWATRCYGGWRGSLFLELPRCDGPLS RWGWAAPKMAASLLFSDQGFLASWIP RNGTLGHAMSGIALLEAVGHGRELWN PATSAASVISNTSSDANQFPKLPLGEISP DKEKSYWSSNPTKNNPKETTRVAVFA RILDVNDNAPHFAVFYDTFVCENARPG QRDACGRLGDWDSEKQEGRKGFSTN SVILHKKRTKRSVLGGDKFWQKSPES PQGDFQDSRSLRSTVKFHKSTRKLQGE VEKSSVARNYGFDPL
330	B	44	329	GCLEHEASSAYEWLWSLCALLDMYTA GPTKTQTLQPMGQPNLKGDDGFTRES TGFMQLPADFISSLICHETWVPGKPSTA MHRGRYWAEPIMLPKX
331	B	3	431	MSEKNTPLVLSGENQKKGREIGVCRK QSQCDHQDNNSHTLRFSSYSSSSGPVT LVSFHSNYPKSVLLQGNLDTETCTER RQREIWTQRHEGKCGHRDMYREKTK RKYREKAIYKLRKGPETDPSSQPSE NPANTLISDS
332	A	5	1269	TISWRQGRGGEAGRRLWHTPPQVKHL EPGHP/EQQARKAQIQGPAPGWDLT QGEQAG/NIHQHCGQSRG*QQHQKDP* GHRFAEGMQSLSKELQSD*TSRKGGFR VPCSHNREPPTRPGDPCDS/PAGLGLQE CRARYRPGKPSS/PPRGQSRAT/GPVRW HPSPSRN*G/PPGSRPAPGTDPA GRPP\

SEQ ID NO:	Method	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion)
				GRPLAASGILLPNSPPAPG/SP/QGPPPPR GSNR/PRFPHWLRRPAGRGAPC*PQPRS PQ/QHIPEHRTKPVPAPEPPSGSRNTDPP GQPRARGTGWKASPGHRADSASRRASF LFRCLANLQRSLKQMRGKLHSQKAQF WFILNGFIGGVIGRRMTDCQACEPRLR SIQCQLPESYTSLCHPAALTQSGPKNVL ERDQPSACSLKTPAQTCLPQCSLHWTL RDDQTQPLTAPSSTMNGAYRMKC
333	A	233	380	PLVVCLLEFYCTHLRDGLNSVQLAYR GCRPTEATFTPARRPWQARAPCR
334	B	220	309	MAEYDLTTRIAHFLDRHLVFPLLEFLS VKE
335	A	577	945	RGARIRYAVCVVCVCVCVYPCVHVCTC VRMCLCVCVCVCVCVCVCGGCKCTC GPTEGGEKAWLFTSIQEGRRCGWSSSL RGSAAGRDLYSARLFAHRLLLLEGRP WQDAGAPSAARISRSEPWS

CLAIMS

WHAT IS CLAIMED IS:

- 5 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-84, or 168-251, a mature protein coding portion of SEQ ID NO: 1-84, or 168-251, an active domain coding portion of SEQ ID NO: 1-84, or 168-251, and complementary sequences thereof.
- 10 2. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under stringent hybridization conditions.
3. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said
15 polynucleotide has greater than about 90% sequence identity with the polynucleotide of claim 1.
4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.
5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the
20 complementary sequences.
6. A vector comprising the polynucleotide of claim 1.
7. An expression vector comprising the polynucleotide of claim 1.
25
8. A host cell genetically engineered to comprise the polynucleotide of claim 1.
9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively
associated with a regulatory sequence that modulates expression of the polynucleotide in the host
30 cell.
10. An isolated polypeptide, wherein the polypeptide is selected from the group consisting of:
(a) a polypeptide encoded by any one of the polynucleotides of claim 1;
(b) a polypeptide encoded by a polynucleotide hybridizing under stringent conditions
35 with any one of SEQ ID NO: 1-84, or 168-251; and

- (c) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 85-167, or 252-335; the mature protein portion thereof, or the active domain thereof.
- 5 11. A composition comprising the polypeptide of claim 10 and a carrier.
12. An antibody directed against the polypeptide of claim 10.
13. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- 10 a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and
- b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.
- 15 14. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions;
- b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and
- 20 c) detecting said product and thereby the polynucleotide of claim 1 in the sample.
15. The method of claim 14, wherein the polynucleotide is an RNA molecule and the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.
- 25 16. A method for detecting the polypeptide of claim 10 in a sample, comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex; and
- b) detecting formation of the complex, so that if a complex formation is
- 30 detected, the polypeptide of claim 10 is detected.
17. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10 under
- 35 conditions sufficient to form a polypeptide/compound complex; and

b) detecting the complex, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.

18. A method for identifying a compound that binds to the polypeptide of claim 10,

5 comprising:

a) contacting the compound with the polypeptide of claim 10, in a cell, under conditions sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and

b) detecting the complex by detecting reporter gene sequence expression, so
10 that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.

19. A method of producing the polypeptide of claim 10, comprising:

a) culturing a host cell comprising a polynucleotide sequence selected from
15 the group consisting of a polynucleotide sequence of SEQ ID NO: 1-84, or 168-251, a mature protein coding portion of SEQ ID NO: 1-84, or 168-251, an active domain of SEQ ID NO: 1-84, or 168-251, complementary sequences thereof and a polynucleotide sequence hybridizing under stringent conditions to SEQ ID NO: 1-84, or 168-251, under conditions sufficient to express the polypeptide in said cell; and

20 b) isolating the polypeptide from the cell culture or cells of step (a).

20. The isolated polypeptide of claim 10 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 85-167, or 252-335, the mature protein portion thereof, or the active domain thereof.

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21. The polypeptide of claim 20 wherein the polypeptide is provided on a polypeptide array.

22. A collection of polynucleotides, wherein the collection comprising the sequence information of at least one of SEQ ID NO: 1-84, or 168-251.

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23. The collection of claim 22, wherein the collection is provided on a nucleic acid array.

24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.

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25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.
26. The collection of claim 22, wherein the collection is provided in a computer-readable format.
27. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.
28. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising an antibody that specifically binds to a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.
29. A method of detecting bone marrow cells or tissues in a sample comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form a complex; and
 - b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected
- wherein the presence of the polynucleotide of claim 1 indicates the presence of bone marrow cells or tissues.
30. A method for detecting bone marrow cells or tissue in a sample comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form a complex; and
 - b) detecting formation of the complex so that if a complex is detected, the polypeptide of claim 10 is detected,
- wherein the presence of the polypeptide of claim 10 indicates the presence of bone marrow cells or tissues in a sample.

SEQUENCE LISTING

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<120> NOVEL BONE MARROW NUCLEIC ACIDS AND POLYPEPTIDES

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<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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 <211> 1468
 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<210> 44
 <211> 1827
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (1)...(1827)
 <223> n = a,t,c or g

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<210> 45
 <211> 2435
 <212> DNA
 <213> Homo sapiens

<400> 45

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 <211> 786
 <212> DNA
 <213> Homo sapiens

<400> 46						
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 <212> DNA
 <213> Homo sapiens

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<211> 1622
 <212> DNA
 <213> Homo sapiens

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 tt 1622

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 <211> 1219
 <212> DNA
 <213> Homo sapiens

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1219

<210> 50
 <211> 1241
 <212> DNA
 <213> Homo sapiens

 <220>
 <221> misc_feature
 <222> (1)...(1241)
 <223> n = a,t,c or g

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<210> 51
 <211> 811
 <212> DNA
 <213> Homo sapiens

<400> 51
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 <211> 688
 <212> DNA
 <213> Homo sapiens

<400> 52
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 <211> 323
 <212> DNA
 <213> Homo sapiens

<400> 53
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 aaccctgagc atcatcgggt gcgcccacca cttctgtatg tgactcaaag taagtgttaag 180
 gaaatccagt tctgttttgc ttctgaaata ctatagtgca ggaagggtgt ttaggtgtca 240
 ggctttgggt gcctacactg tgctttcgga attattcact gaggcgaaag aacagagatt 300
 agctactgat gaaggacaaa aag 323

<210> 54
 <211> 339
 <212> DNA
 <213> Homo sapiens

<400> 54
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 aaccctgagc atcatcgggt gcgcccacca cttctgtatg tgactcaaag taagtgttaag 180
 gaaatccagt tctgttttgc ttctgaaata ctatagtgca ggaagggtgt ttaggtgtca 240
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<210> 55
 <211> 1187
 <212> DNA
 <213> Homo sapiens

<400> 55
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 catacatgct ctgaaaataa gtgtctttta gttgtgtttt tctgtgtgac atcatctctg 180

aacttgaaca	tgttcattac	ggcaagattg	taatcctgct	gtattcctcg	ccctccgtat	240
tctatccctt	taaaaactag	atatttaaac	atatttatcct	aatgtgtttc	atcagaacac	300
tttgacact	ttcttactaa	aacggtatgt	gggtggtccg	agacagaatg	gtacctacag	360
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cgctgccctg	gtccagacta	cccttgcttg	cgtcagtcaa	aactgttgta	actactttga	1140
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<210> 56
 <211> 327
 <212> DNA
 <213> Homo sapiens

<400> 56						
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gatttagccc	acatcttttg	ctttggtttt	gcacacagct	gctgctggga	gctggggcca	180
gggcaggcag	aaataatcct	gggctctgca	gagcctgttt	caggctcatg	gtctacccta	240
ccccgcccc	atttccggca	aaaccaggct	gagggtggg	ctgctagcga	agctgacagc	300
aagagtgaca	gccctgtcct	gtcgctg				327

<210> 57
 <211> 1471
 <212> DNA
 <213> Homo sapiens

<400> 57						
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cttccctttc	aggtgtctct	cgctgtctg	cagatatcag	accccagctc	atctcagacc	180
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gccacatgt	cccagaaggc	agggggcttt	cgcaacattg	caatccaaac	ttcccccagt	300
ctcaggaagc	atttcccagt	tttcaaaagg	aagagactca	cagccagtaa	gtccctgggtg	360
gaaatgccaa	cagcctccca	aagtgccatc	caggctcaacg	gtaacctctc	tgaacaggac	420
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gttagcatat	gcttggaagc	aggaacttgg	aggtccttag	agaaagccac	agctgccatt	600
caggttccag	atgatattta	tcacagtcct	tcctgggaag	ctagagagtc	tgctctcagc	660
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ccaggaagag	cctcagactg	tccttcatca	agtaacaatc	accagaatct	ggtgtcactc	1020
aaaactaaca	gtgcacgaa	atctgccctt	gggtgtcagg	agcagacggc	aaacaacccc	1080
accgagtcag	acacactgga	gtttccaaat	tgtccaggaa	gtaatcatct	cccctcctct	1140
ctttcaaggga	gtgagaccaa	acttcagagc	aacagggaga	ttagtgacat	taatcaaatt	1200
cacctggcac	gggggtgaact	ctgcgacctc	caaggccgac	tgcaatctgt	ggaggaaatct	1260

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gctcgagctc	tcactgaagg	cctccttggc	tctcctctta	ccattgaaca	cttggatata	1380
tcctatctca	ccaagagcac	agacccaaca	ccaatgccta	gagattctat	ccatggctct	1440
caggagcttg	cagggatttc	cgtacataaa	g			1471

<210> 58
 <211> 811
 <212> DNA
 <213> Homo sapiens

<400> 58						
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tttcaccttt	tgacaatggc	aaaagcaaag	tttgaagggtg	ctgagtctgt	ggagccagtg	300
tcaccttcac	agcccaaaag	gccatcctat	gtccccctag	aagagctatg	gacgaggtta	360
acaaaaggga	acagcaggcc	tcagcagagg	gacagggaga	agggaggatg	gatgaaggga	420
gtgcagcaag	gccatcaagg	agtaggaaag	caggagggaag	gttcagagaa	catcaaagaa	480
aaagctggta	actggggaga	tgggaggagg	tggggaaagaa	atcagcagggt	tttgattaat	540
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agctattttt	gcaatgcgta	ttccttgagt	tggactcata	ttgtcctaca	tcattgtgaa	660
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catgcactat	cagttacttc	agaacttggg	gcagatatca	gcagacttgc	aggggttgat	780
gagggcatata	aacttacaag	tattggctct	g			811

<210> 59
 <211> 593
 <212> DNA
 <213> Homo sapiens

<400> 59						
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gagcgcgaaac	ttgcggagca	ctttgcatgc	gcgccgcggg	taggactgga	cggctcggatt	120
tgtaggcaat	tctgacaccg	agctcccggg	ctcggttggc	agaagatcgc	tttgggaatc	180
ctcctactct	acgaggacca	gaaaccaagg	acgccaaagcc	atacaaatc	agcacagctg	240
actcagagag	gtggaaagga	aatcaggaca	aaaagccaca	atgtcttctg	gaggaggata	300
ttgccagcca	gaataactgt	gagagatgta	ggcaagcata	gtcctggaaa	caaacagcac	360
aattccttta	aagccctaaa	ggatgaagat	cttctgttag	agaagtattt	aatggaaagg	420
cagcctgtag	gtgagccagc	tgcgcaccag	gtagctatgg	atgtgatgca	cagcccatc	480
ctccaactgg	aaaggaaaca	caaagtctca	agtgacagca	accagacaga	gactactgca	540
gagaagttgc	cagaggactc	tttcttaaaa	aacaagcaaa	aacaggttta	tat	593

<210> 60
 <211> 538
 <212> DNA
 <213> Homo sapiens

<400> 60						
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ataagagaat	actatgaaca	attccatata	cataagttta	caaagattgg	aaatgcttat	120
gctgttttaa	gtaatccaga	aaagcgaaaa	cagtatgacc	tcacgggcaa	tgaagaacaa	180
gcatgtaacc	acaaaaacaa	tggcagattt	aatttccata	gaggttttgt	gaagltgata	240
taactccaga	agacttgttt	aatatatttt	ttgggggtgg	atttccttca	ggtagtatac	300
attctttttt	aaatggaaga	gctggttata	gccaaacaaca	tcagcattga	catagtggac	360

atgaaagaga	agaggaaaga	ggagatggag	gtttttctgt	gtttatccag	ctgatgccca	420
taattgtatt	gatcctcgtg	tcattattaa	gccagttgat	ggtctgtaat	cctccttatt	480
ccttcctatcc	cagatctgga	acagggcaaa	ctattaaaac	gcagacagaa	aacttgagg	538

<210> 61
 <211> 816
 <212> DNA
 <213> Homo sapiens

<400> 61						
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gcaaaggaga	gtgggcgctc	cctttctctt	cctggaagat	cagtcccacc	ccccatttct	180
acatctcctt	gggtatacca	gcctacttat	agttactcta	gtaaaccaac	cgatggacta	240
gagaaagcaa	acaagagacc	aactccttgg	gaagcagcag	caaagtctcc	tctcgggtcta	300
gtggatgatg	ctttccaacc	cagaaacatc	caggaatcca	ttgtggcaaa	tgtgggtttca	360
gcagctcgga	ggaagggtgct	tccagggcct	ccagaggatt	ggaatgaaag	actgtcctat	420
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cttcagtag	ctgattacaa	ctacaaccca	cacccaaggg	gatggagacg	ccaaacatga	660
aaagttagaag	aacggatcat	gtgccaaactg	tagtttttta	aaaaaaacgc	tcctttgtag	720
ggttttaaac	ttttcttaata	gatttagatt	cacttttggg	cttggcttgt	tctcataaagt	780
catttatcta	agtttgtgtt	tctgtgtgtg	tgagtg			816

<210> 62
 <211> 646
 <212> DNA
 <213> Homo sapiens

<400> 62						
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aaggcagttt	gcaaaagagg	accagtctct	ggcagaggat	tttgggtgta	aacatgctgt	120
atcggtctgt	ggtgggagtg	cgtatcagca	ccacccccgt	ggaaggctac	ttgatgcgga	180
taagttccat	ccactggcaa	acccaaaagc	tacacatgtc	tacatgggaa	gggctgtgcg	240
gcacagggtgc	acagcagatc	tcagcgctct	tcccctgatg	tttctgctct	tcccatgcac	300
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gtgtgtgatc	ctgcgccaca	acttggccag	ccggcctgga	cagctggctc	tggttactgt	480
gggaacaatg	caaggaaggc	cgttgtcaca	ttcctctgag	gtcaaaggca	caaccttcgt	540
cacacactca	gtccctgctg	gcaaagagaa	agacgaggag	cgtggaatcg	gagacctgga	600
gcatgcgagg	gacttgagaa	attcaccaac	tcccttgttt	tactga		646

<210> 63
 <211> 590
 <212> DNA
 <213> Homo sapiens

<400> 63						
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gtatgaggtc	agatggttgc	ttgtaagtgt	tttcaaactg	ctaaggagcc	ttctgttgga	120
gcttgggagt	cagaaacctg	ggtctcacct	ggctctgtga	agtactcaca	tggcctttga	180
ccttggccaa	ctcacttaac	cttgttgagt	gaatgagagt	accatggagt	aagtgccttga	240
gtcgaggcat	gcctttgcct	tctcagaggt	tatggttaag	tgaattaata	tatctgaagt	300
tcttagcatc	aggtctgttt	aatggttatc	ccaatccaga	aaatttttcc	tggacagaat	360

acctggaagc	tactcaaacc	aatgcagttc	ctgccaaagt	ttttaaaatg	gacagtgatg	420
ttggggagaa	cagaaagatt	ctccgggatg	aaagacctaa	ttacagtcag	tatactccat	480
ttagtagatg	tgataatgca	tcttacaaag	aaaatgtgtt	tctacaaaag	ctggagagaa	540
acacaccaga	tattgcagaa	agatttgact	gtttattact	gacatattag		590

<210> 64
 <211> 386
 <212> DNA
 <213> Homo sapiens

<400> 64						
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tgctgggaag	cctttgggtc	atgctacctt	ccctggttca	gttagctata	gctaggagaa	120
aagtgtggcc	ctttggtcca	gaacctggcc	acctgatctc	tgaatttggg	cattttgaag	180
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aggggatggg	ctggttgacg	attgactttt	ctcctcaagc	atctaaacgt	gccctaacgt	300
cttccattat	ggagctgggg	ccaggtgtca	gcaaactggg	tcagtggcag	ctggagaacc	360
taaaaaggca	ttgtgggcct	ctgtag				386

<210> 65
 <211> 615
 <212> DNA
 <213> Homo sapiens

<400> 65						
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tttctgctgc	tgtgaagaaa	tgagcaggga	gggtggcaagt	gtgtgggtga	taatgacaac	120
taatgttttt	gagcagttag	tctgagtcag	gccttatgcg	atgcaaggtc	catgcaccgt	180
cttattcaaa	ccttccacac	ctgtaagggg	ttctctttaa	tcaaccattt	gtacaaatga	240
gaaaaccaag	acttgtgaag	atthttgcagg	ttgcccaagg	tccccataga	ttaagagata	300
aagcaagact	tcaaatccag	gccagtgtga	ccctggagtg	tgtggactca	cccctgcagt	360
acactacctc	tcaccatcct	tgtaaaaaga	aaaagttaagt	tgtcagggca	agagcactga	420
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agggaaatgg	gatgg					615

<210> 66
 <211> 613
 <212> DNA
 <213> Homo sapiens

<400> 66						
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tcagggtgct	tgctccatgc	tcgctccaca	cctggggctc	aacctgggt	ttccccggct	180
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tagttcagtg	ccagcacgag	atgggaggcc	catgaagtta	gcagtgcaca	aaaaatagag	360
caaagactgg	atgcatttcc	tgagaacaac	catcactgta	aagcacttta	caaatccaaa	420
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ctctaaaaac	attacaagtt	agttcatgtc	atgccagata	gctgaaggca	gcttcacaag	540
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<210> 67
 <211> 930
 <212> DNA
 <213> Homo sapiens

<400> 67
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 cagtatgacg acgatgcttt catggtgaag tttgtgcat cttctactga acatttttta 720
 aacaaccccc aaacagatgc agttttgggc cagcgttatg gaagagaaag caaatcccc 780
 aaatgtctga atcacaaaca cagagacctc acccccgtag cagtggaaac aaatgcctg 840
 gcctctgacc cctacagatc cgcgttcctg ccctaaacg gtgcagttag gggagagctg 900
 ggctgcagaa cagggtggaga gaagaacgtg 930

<210> 68
 <211> 239
 <212> DNA
 <213> Homo sapiens

<400> 68
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 ccgtgtcagc tgcagagact ggagtcggg gcatgatggg gatgtacctg aaacctagtg 120
 agagtcatcc tgactctggg gaagagccgc tcaaagatga gaaagataaa ggggtaacca 180
 gaggtggtgg tgtggtccac tgtgactcgt cagctgttgc tctgtgtgtt catttttga 239

<210> 69
 <211> 336
 <212> DNA
 <213> Homo sapiens

<400> 69
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 tttctatttc atgctgttta atagggttg ctgtgaatcc gtgctacct tgaatttttc 180
 agcacagtaa atgtaagact tctagacatc tgcaagaagc atataagtaa aagagctcca 240
 ctgtaatgag aatggcatta gactcatgca tgcaacttta ttcagtcttt cctttgtgtc 300
 acctcaacac atcaatgggt tgacaagtga aaaagt 336

<210> 70
 <211> 489
 <212> DNA
 <213> Homo sapiens

<400> 70
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 tctgataag 489

<210> 71
 <211> 362
 <212> DNA
 <213> Homo sapiens

<400> 71
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 cggtagcccat agtggaagcc acttgcagta tgccctggcc agctgcagcc tcacacagag 180
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 gcacagtggc cagacctcac ttgcagacct ctcatgctg cacatctggc ttgcccttgg 300
 cagacatgga atccaggctg gttgcttcac caagttagtg gaacaagctc acttgggccc 360
 ag 362

<210> 72
 <211> 265
 <212> DNA
 <213> Homo sapiens

<400> 72
 aatgagccta tagaaaaaca cacacacaca ctgaagataa tcagggtcac tgaattgaat 60
 gtgatttttg gtgagattga aattgtgcaa gtccaggcct atcagtgga agtaggagga 120
 ggagatgatc agcagtgtt tccctcctcct aacccttacc cggctcttacc tgctgctgcg 180
 gtatcaaac accacatcga tgacagaatt ggaccacgc aggctgcact gcaccatctg 240
 gatggaagtg tagaggcctg caaag 265

<210> 73
 <211> 390
 <212> DNA
 <213> Homo sapiens

<400> 73
 ttctgtgtga caaaaggga ggacaagtga gtggctgcat gaggataaaa atgccctttg 60
 gcaacagctg tattcagtga gcctcttccc cagaggatac gccctccctg cttcctgggc 120
 agagccgggg cttgaggtca gctgggtgga agatgagcag ggcctccctg atcctggctt 180
 cttggagaag agccccctcc ctttctgtgc agaaggcag ccagactgct agacacacct 240
 gccaccaga gggtccgctg ggaaactgct tcttacctgt ctacaaggcc agtccccca 300
 cagttaccgc tctttgggct gaaaggtaag aggggagggg ggtgacggac tctgctgggc 360
 acttggctct tccactgagc aactcacacc 390

<210> 74
 <211> 362

<212> DNA

<213> Homo sapiens

<400> 74

cccatgtggt	gaactgctgc	ccatcctcaa	aaaaaaccag	ttaaaccatcc	ttctcttgca	60
accagtggac	acagagactt	tggaagggcc	tccaggcctt	ggcctggatg	cagagggccc	120
tgagaagaga	cacaggtggc	agtcagtctg	actatcctct	cgccctgtcc	tcatttccca	180
cagctggatc	ctcctgccct	gccctgggat	tgaccacacc	tctggcttgg	aggttatgtc	240
tgatctttat	cacaggaagg	gaaactcgct	ccatccccaa	ggaaagagaa	ccaaggatgc	300
cagaaaggaa	agcttccccc	agaagatggg	acaatttccc	ttacaaagtc	tggcagtcac	360
ct						362

<210> 75

<211> 340

<212> DNA

<213> Homo sapiens

<400> 75

atgcttcttg	ctgacaaaga	ggcctctgaa	gcaggcctca	ccaatgttcc	caacgatgca	60
aactatccaa	gatacagtcc	agcagagtgc	ttaatggcca	taggctttgg	tgtccggaag	120
tctaggttgg	agcacttgca	tctgcaacag	tgtgcagggtg	atcttctctc	tgcaagcctc	180
agcccaacta	accagatatc	agtatctgtg	tgggcacata	tccataagct	ggcccgtggg	240
aattcttaag	tacgctgcga	gcgtctatgg	tatttctcta	gcagaccgta	agcgacaata	300
tgacagatac	tttcgatatg	aacgtttacg	caccataaag			340

<210> 76

<211> 390

<212> DNA

<213> Homo sapiens

<400> 76

tttcgtggga	gacgcaagcc	aggaggccag	ggctcctctt	cggctgcccg	ctgctgagat	60
gggcgcggca	gccaaggggt	cgttgtgggc	ctccccttcc	tctcgttcag	tgctgcccct	120
ttgtcttggg	tccagtctct	gactcctcgt	agctgctcgc	ttggaccagg	ctggccgtgg	180
tgacagcact	gtgtcgtccc	cgtcctcagg	cagtgggcct	tccgggtagt	agcggctcag	240
tcccgccctag	gctctcagga	ctccacagcc	cctgagtatt	tgactcaaat	caccagtcca	300
atatccctcc	cgttaccagt	gaggaacctg	gggccccagag	aagaggacgg	agtcctgccc	360
aagtgactca	agaccctctt	aggaacttct				390

<210> 77

<211> 614

<212> DNA

<213> Homo sapiens

<400> 77

tttcgtaaga	aatgaagcca	gagagtggc	ctgggggcag	accatggatc	tctttggaca	60
tgccaacaag	tttgggtttt	attctgattg	aggagggtca	tatattgtgt	catttattct	120
tcacagccac	ccatgaggct	aattttatcc	ctatttatag	atgaagtgcc	tgaagcttag	180
agggggctta	gttaagggtca	cataactgg	aagtgatagg	gctgggggtt	gaccacctgc	240
tctggatgcc	aggatctgtc	cttttcagct	acagctgctc	cttggaagct	gccagtagaa	300
aatctgctgg	atgcttttca	gtgattctgg	tgtaaaactt	caaaggatgc	tttgggtggt	360
tgtgagagca	gatttgaaag	atggtggtgg	taacaaattg	ggtccaaacta	tataggtcct	420
gtgagttcag	ggtaaggat	gaggtgcttt	tgctatagag	aaccctggat	ccaaaggaga	480
ggaccctgctc	agagtctgag	gggaactgct	ggtagttaga	gtcagaaagc	atgttcacac	540

tggtggaaga	gggttagacca	caggtaaata	gggttgtag	atggaggtaa	ctgttgga	600
tccgggaaaa	tggtg					614

<210> 78
 <211> 627
 <212> DNA
 <213> Homo sapiens

<400> 78						
cgctccattt	ttcttttccc	caaatacatc	taagataaaa	ttgtggatat	cagaaggttc	60
ataggggtcc	cccttccacc	agcctgccaa	ggagaattct	gcagtccctg	gcccagcttt	120
ccgcctcat	ccctggagag	ggatgcctgt	ggaaggcttg	gtgattggga	ctcagagaaa	180
caggaaggga	gaaaagggtt	cccctccacg	aattcagtca	ttctacataa	aaaaagaaca	240
aaaaggagtg	tggtgggagg	ggacaagttt	tggcaaaaaa	aatctccaga	aagtccacaa	300
ggggacttcc	aggacagtag	gagcctcagg	tccacagtga	agtttccac	gtccacaagg	360
aagttgcaag	gggaagtgga	aaagagcagt	gttgccagaa	attatggatt	tgatcctctt	420
taatgcctgt	gaagatacac	aaaaacatga	aatttctttt	caatattttt	gggctgaacc	480
acttgggtgg	tggtgaaat	gagaccatac	atacagcaca	atgcatgtct	gttatattgc	540
aaagtgtatt	acctaggtct	catacatccc	cctagtcac	agcattaatg	catgttggga	600
ccccgacca	cacaagcaga	agtaatg				627

<210> 79
 <211> 255
 <212> DNA
 <213> Homo sapiens

<400> 79						
cacagcccga	ggtccgtggc	aggaggagat	gacaagcagg	gagaacacca	acggaataaa	60
ctctgcagtt	tccttcagat	catccctgca	taggtgtttc	tcgaaactca	tgttcagtga	120
gaacagcaga	catagactca	ggacaaaacc	tccgtctcct	ttcaggttag	gttggcccat	180
gggctggagc	gtctgcgtct	tggtcggccc	ggcagtgtac	atgtcaagca	gcgcgcaaag	240
actccacagc	cattc					255

<210> 80
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 80						
aaacaacttc	agttccatct	gatgtagctg	actttttgat	gagactaaaa	ctgtgtagtt	60
catcatctcc	atccaagttc	agatctcaag	tctatgatct	tgactacott	aatgtatggc	120
tattattatc	ttgatgatca	cattggcttt	gctttcggca	caccccgatc	tctctccott	180
tcttctgatt	ttctccactc	aaaacaagag	gggtattttt	ctccgacatt	g	231

<210> 81
 <211> 415
 <212> DNA
 <213> Homo sapiens

<400> 81						
tttcgttggg	tagtcacttt	tcaaaggtea	catgtccott	gcttggaccc	catcacacac	60
aacctgctgg	tagtgtctgc	ctcctgacag	gtgccactgg	ccatgggctg	tgggagccca	120

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gaggettcga aggacccctt cagcatttca tgcgataggc tccattcatt gtactgctcg   180
gggctgtgag tggctgcgtc tgatcgtctc ttaatgtcca gtgtaggagg cactgaggca   240
ggcaggctctg agcaggctga aagggggatt ggtgtatcag agagagtagg agtccaggct   300
caggatcgga cagagctgag tgcagattgc aacactgtga ctcccaaggc caaggcttcg   360
tgatcttggg aggttattta aaagaggccc tatggtgtcg tggttaagagc atggg      415

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<210> 82
<211> 291
<212> DNA
<213> Homo sapiens

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```

<400> 82
gtcaagtgtc acccgttgca ggcgagggg ccacgcgggt ctggttgga gatcgagcct   60
ggctgatccg ttttgggcgg aagagtagga tttattcctg aaagtgtgga ggcgagcg   120
tttgggtccg aagttgagtt gcaggagat gtgtggcctg tggaccatgg ctcttttact   180
gcaaagttct tttgcttatt tctgaaactt acattgttta ttcgctactg ggctggagaa   240
gccaatgtga cagaatttaa accgtctctc agatgtgtac agtagaactc a          291

```

```

<210> 83
<211> 426
<212> DNA
<213> Homo sapiens

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```

<400> 83
aatcaaaaag ctctaacagc actccaggtt gcttttacia gccagcctgt gaagctctaa   60
cgttctctag cgaaaccagc gaatcgccaa ctccgagaa gaaatgatgc gaaaatccct   120
cccgactga cacctcagta agtgaaagag acttcttttc tctctccgta acctccctcc   180
tctcactgc cgaatagtgc ggtgcttctt aactgagacg acgctaaact accagaagat   240
ccttagtgtc cgtccaggaa ccaaactcgc gaccgcctcg cacgtgtcag gcctaggact   300
acagacacca cctttcggcc ttgctcagca cctcatccgc cccacgcct tctttgcgcc   360
caaagacccc ctacactcct ttacagagag aaattcaaga agcgacgaaa tcgtcgacct   420
gggaat

```

```

<210> 84
<211> 58
<212> DNA
<213> Homo sapiens

```

```

<400> 84
tttttttttt ttaaagtata aaattttttt ggaaaaaaag gaaaaaaatc tatataaa   58

```

```

<210> 85
<211> 101
<212> PRT
<213> Homo sapiens

```

```

<400> 85
Met His Cys Gln Lys Lys His Pro Tyr Trp Tyr Gln Gln Lys Ser Gly
 1             5             10             15
Gln Ala Pro Val Leu Val Ile Tyr Glu Asp Asn Lys Arg Pro Ser Gly
          20          25          30
Ile Pro Glu Arg Phe Ser Gly Ser Asn Leu Gly Ile Met Ala Thr Leu

```

```

      35          40          45
Ile Ile Ser Gly Ala Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr
      50          55          60
Ser Thr Asp Ser Ser Gly Asn His Arg Glu Val Phe Gly Gly Gly Thr
      65          70          75          80
Arg Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Phe Gly His Ser
      85          90          95
Val Pro Ala Leu Leu
      100

```

<210> 86
 <211> 57
 <212> PRT
 <213> Homo sapiens

```

      <400> 86
Met Arg Lys Glu Gln Glu Val Thr Lys Lys His Ile Cys Glu Leu Leu
      1          5          10          15
Thr Glu Thr Val Thr Ser Ala Glu Thr Pro Asp Ala Leu Ala Lys Ser
      20          25          30
Arg Tyr Arg Ser Lys Leu Ala Asn Gln Met His Phe Leu Gly Leu Lys
      35          40          45
Tyr Arg Trp Val Leu Ile Phe Arg Met
      50          55

```

<210> 87
 <211> 99
 <212> PRT
 <213> Homo sapiens

```

      <400> 87
Met Ala Leu Val Ala Ser Pro Ser Met Gly Arg Asn Leu Lys Asp Glu
      1          5          10          15
Lys Leu His Pro Lys Ala Tyr Gly Ser Trp His Leu Val Pro Trp Gln
      20          25          30
Met Leu Asp Pro Asn Thr Asn Gly Ser Pro Val Phe Pro Ser Ala Leu
      35          40          45
Pro Lys Thr Gly Val Val Gly Trp Gln Ser Met Trp Cys Phe Gly Lys
      50          55          60
Val Lys Glu Gly Met Asn Ile Val Glu Ala Met Glu Arg Leu Trp Val
      65          70          75          80
Pro Gly Met Ala Arg Pro Ala Arg Arg Ser Pro Met Leu Thr Val Asp
      85          90          95
Asn Ser Lys

```

<210> 88
 <211> 144
 <212> PRT
 <213> Homo sapiens

```

      <400> 88
Met His Glu Val Asn Ala Lys Ser Cys Cys Arg Val Pro Cys Gly Lys
      1          5          10          15
Arg Val Ala Arg Lys Leu Arg Glu Asn Gln Gln Ala Leu Trp Arg Pro

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```

          20          25          30
Lys Ala Pro Glu Asp Val Arg Pro Gly Asn Gly Leu Glu His Arg Pro
          35          40          45
Gly Gly Asp Pro Gly Ala Ala Glu Pro Asp Ala Val Cys Ala Ser Arg
          50          55          60
Pro Ser Thr Glu Gln Arg His Gly Arg Ser His Gly Ala Arg Thr Pro
          65          70          75          80
Gly Lys Thr Thr Arg Gly Ala Phe Ser Pro Arg Pro Pro Ala Pro Ala
          85          90          95
Phe Ser Ser Arg Leu Val Gly Leu Asn Pro Thr Pro Ala Phe Ser Leu
          100          105          110
His Phe Met Ser Phe Pro Gln Lys Tyr Ile Gln Lys Met Pro Phe Phe
          115          120          125
Pro Leu Val Thr Leu Ile Pro Gly Phe Ser Pro Phe Ser Gly Ser Leu
          130          135          140

```

<210> 89
 <211> 59
 <212> PRT
 <213> Homo sapiens

```

          <400> 89
Met Cys Asn Gly His Val Trp Leu His Asp Arg Tyr Trp Asp Ser Gly
          1          5          10          15
Ala Pro Arg Trp Gly Glu Glu Phe Ser Leu Ser Lys His Pro Gln Gly
          20          25          30
Thr Glu Val Lys Ala Ile Thr Tyr Ser Ala Met Gln Val Tyr Asn Glu
          35          40          45
Glu Asn Pro Glu Val Phe Val Ile Ile Asp Ile
          50          55

```

<210> 90
 <211> 78
 <212> PRT
 <213> Homo sapiens

```

          <400> 90
Met Gly Gly Gly Gly Leu Arg Arg Gly Pro Glu Gly Glu Leu Gly Glu
          1          5          10          15
Gly Arg Lys Arg Lys Ser Ser Ala Arg Val Val Glu Lys Lys Ser Pro
          20          25          30
Pro Pro Ser Ala Tyr Thr Glu Ala Ala Thr Arg Leu Phe Ala Ser Pro
          35          40          45
Thr Pro Pro Ser Phe Ser Gly Arg Gly Leu Leu His Pro Trp Ala Gly
          50          55          60
Thr Arg Tyr Phe Ser Pro Ser Ser Ser Leu His Pro Arg Ile
          65          70          75

```

<210> 91
 <211> 1089
 <212> PRT
 <213> Homo sapiens

<400> 91
Met Asn Leu His Ser Thr Leu Gln Val Ile Ser Leu Gln Val Asn Asn
1 5 10 15
Leu Asp Ile Ile Val Ile Pro Glu Thr Ser Val Glu Leu Ser Gly Phe
20 25 30
Leu Gln Lys Ser Phe Pro Lys Glu Lys Asp Asp Leu Ser Pro Gln Pro
35 40 45
Leu Met Thr Val Cys Glu Arg Ser Phe Arg Glu Gln Gly Ser Phe Gln
50 55 60
Ser Thr Tyr Glu Arg Ile Thr Glu Val Ala Val Glu Ile His Arg Met
65 70 75 80
Asn Leu Val Leu Leu Arg Thr Val Gly Met Ala Asn Arg Glu Lys Tyr
85 90 95
Gly Arg Lys Ile Ala Thr Ala Ser Ile Gly Gly Thr Lys Val Asn Val
100 105 110
Ser Met Gly Ser Thr Phe Asp Met Asn Gly Ser Leu Gly Cys Leu Gln
115 120 125
Leu Met Asp Leu Thr Gln Asp Asn Val Lys Asn Gln Tyr Val Val Ser
130 135 140
Ile Gly Asn Ser Val Gly Tyr Glu Asn Ile Ile Ser Asp Ile Gly Tyr
145 150 155 160
Phe Glu Ser Val Phe Val Arg Met Glu Asp Ala Ala Leu Thr Glu Ala
165 170 175
Leu Ser Phe Thr Phe Val Glu Arg Ser Lys Gln Glu Cys Phe Leu Asn
180 185 190
Leu Lys Met Ala Ser Leu His Tyr Asn His Ser Ala Lys Phe Leu Lys
195 200 205
Glu Leu Thr Leu Ser Met Asp Glu Leu Glu Glu Asn Phe Arg Gly Met
210 215 220
Leu Lys Ser Ala Ala Thr Lys Val Thr Thr Val Leu Ala Thr Lys Thr
225 230 235 240
Ala Glu Tyr Ser Glu Met Val Ser Leu Phe Glu Thr Pro Arg Lys Thr
245 250 255
Arg Glu Pro Phe Ile Leu Glu Glu Asn Glu Ile Tyr Gly Phe Asp Leu
260 265 270
Ala Ser Ser His Leu Asp Thr Val Lys Leu Ile Leu Asn Ile Asn Ile
275 280 285
Glu Ser Pro Val Val Ser Ile Pro Arg Lys Pro Gly Ser Pro Glu Leu
290 295 300
Leu Val Gly His Leu Gly Gln Ile Phe Ile Gln Asn Phe Val Ala Gly
305 310 315 320
Asp Asp Glu Ser Arg Ser Asp Arg Leu Gln Val Glu Ile Lys Asp Ile
325 330 335
Lys Leu Tyr Ser Leu Asn Cys Thr Gln Leu Ala Gly Arg Glu Ala Val
340 345 350
Gly Ser Glu Gly Ser Arg Met Phe Cys Pro Pro Ser Gly Ser Gly Ser
355 360 365
Ala Asn Ser Gln Glu Glu Ala His Phe Thr Arg His Asp Phe Phe Glu
370 375 380
Ser Leu His Arg Gly Gln Ala Phe His Ile Leu Asn Asn Thr Thr Ile
385 390 395 400
Gln Phe Lys Leu Glu Lys Ile Pro Ile Glu Arg Glu Ser Glu Leu Thr
405 410 415
Phe Ser Leu Ser Pro Asp Asp Leu Gly Thr Ser Ser Ile Met Lys Ile
420 425 430
Glu Gly Lys Phe Val Asn Pro Val Gln Val Val Leu Ala Lys His Val
435 440 445
Tyr Glu Gln Val Leu Gln Thr Leu Asp Asn Leu Val Tyr Ser Glu Asp
450 455 460
Leu Asn Lys Tyr Pro Ala Ser Ala Thr Ser Ser Pro Cys Pro Asp Ser
465 470 475 480
Pro Leu Pro Pro Leu Ser Thr Cys Gly Glu Ser Ser Val Glu Arg Lys
485 490 495
Glu Asn Gly Leu Phe Ser His Ser Ser Leu Ser Asn Thr Ser Gln Lys

Ser	Leu	Ser	Val	Lys	Glu	Val	Lys	Ser	Phe	Thr	Gln	Ile	Gln	Ala	Thr
		515					520					525			
Phe	Cys	Ile	Ser	Glu	Leu	Gln	Val	Gln	Leu	Ser	Gly	Asp	Leu	Thr	Leu
	530					535					540				
Gly	Ala	Gln	Gly	Leu	Val	Ser	Leu	Lys	Phe	Gln	Asp	Phe	Glu	Val	Glu
545				550					555						560
Phe	Ser	Lys	Asp	His	Pro	Gln	Thr	Leu	Ser	Ile	Gln	Ile	Ala	Leu	His
			565						570					575	
Ser	Leu	Leu	Met	Glu	Asp	Leu	Leu	Glu	Lys	Asn	Pro	Asp	Ser	Lys	Tyr
		580						585					590		
Lys	Asn	Leu	Met	Val	Ser	Arg	Gly	Ala	Pro	Lys	Pro	Ser	Ser	Leu	Ala
	595						600					605			
Gln	Lys	Glu	Tyr	Leu	Ser	Gln	Ser	Cys	Pro	Ser	Val	Ser	Asn	Val	Glu
	610					615					620				
Tyr	Pro	Asp	Met	Pro	Arg	Ser	Leu	Pro	Ser	His	Met	Glu	Glu	Ala	Pro
625				630						635					640
Asn	Val	Phe	Gln	Leu	Tyr	Gln	Arg	Pro	Thr	Ser	Ala	Ser	Arg	Lys	Lys
			645						650					655	
Gln	Lys	Glu	Val	Gln	Asp	Lys	Asp	Tyr	Pro	Leu	Thr	Pro	Pro	Pro	Ser
			660					665					670		
Pro	Thr	Val	Asp	Glu	Pro	Lys	Ile	Leu	Val	Gly	Lys	Ser	Lys	Phe	Asp
	675						680					685			
Asp	Ser	Leu	Val	His	Ile	Asn	Ile	Phe	Leu	Val	Asp	Lys	Lys	His	Pro
	690					695					700				
Glu	Phe	Ser	Ser	Ser	Tyr	Asn	Arg	Val	Asn	Arg	Ser	Ile	Asp	Val	Asp
705				710						715					720
Phe	Asn	Cys	Leu	Asp	Val	Leu	Ile	Thr	Leu	Gln	Thr	Trp	Val	Val	Ile
			725						730					735	
Leu	Asp	Phe	Phe	Gly	Ile	Gly	Ser	Thr	Ala	Asp	Asn	His	Ala	Met	Arg
			740					745					750		
Leu	Pro	Pro	Glu	Gly	Ile	Leu	His	Asn	Val	Lys	Leu	Glu	Pro	His	Ala
	755						760					765			
Ser	Met	Glu	Ser	Gly	Leu	Gln	Asp	Pro	Val	Asn	Thr	Lys	Leu	Asp	Leu
	770					775					780				
Lys	Val	His	Ser	Leu	Ser	Leu	Val	Leu	Asn	Lys	Thr	Thr	Ser	Glu	Leu
785				790						795					800
Ala	Lys	Ala	Asn	Val	Ser	Lys	Leu	Val	Ala	His	Leu	Glu	Met	Ile	Glu
			805						810					815	
Gly	Asp	Leu	Ala	Leu	Gln	Gly	Ser	Ile	Gly	Ser	Leu	Ser	Leu	Ser	Asp
			820					825					830		
Leu	Thr	Cys	His	Gly	Glu	Phe	Tyr	Arg	Glu	Arg	Phe	Thr	Thr	Ser	Gly
	835						840					845			
Glu	Glu	Ala	Leu	Ile	Phe	Gln	Thr	Phe	Lys	Tyr	Gly	Arg	Pro	Asp	Pro
	850					855									

```

      1010              1015              1020
Leu Lys Ser Glu Phe Val Pro Ser Thr Ser Thr Lys Gln Gln Gly Pro
1025              1030              1035              1040
Gln Pro Thr Leu Ser Val Gly Gln Glu Ser Ser Ser Pro Glu Asp His
      1045              1050              1055
Val Cys Leu Leu Asp Cys Val Val Val Asp Leu Gln Asp His Gly Pro
      1060              1065              1070
Ser Leu Leu Arg Arg Asp Ile Arg Arg Asp Tyr Ser Lys Gly Thr Arg
      1075              1080              1085
Gly

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<210> 92
<211> 182
<212> PRT
<213> Homo sapiens

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```

      <400> 92
Met Ser Asn Glu Thr Val Leu Leu Ala Lys His Asn Ile Phe Thr Leu
  1              5              10              15
Ala Leu Met Ile Val Asn Leu Phe Asn Met Phe Ile Thr Tyr Gly Asp
      20              25              30
Thr Phe Leu Pro Thr Pro Ser Ser Tyr Asp Glu Leu Tyr Tyr Glu Ile
      35              40              45
Ile Arg Met His Gln Ser Phe Asp Asn Leu Tyr Ser Met Gly Leu Arg
      50              55              60
Leu Ser Thr Asn Ala Gly Gln Trp Lys Glu Ala Ala Ser Lys Val Thr
      65              70              75              80
His Ala Leu Val Asn Ile Arg Ala Ile Ile Asn His Phe Asn Pro Lys
      85              90              95
Ile Glu Ser Tyr Ala Ala Val Asn His Ile Ser Gln Leu Ser Glu Glu
      100              105              110
Gln Val Leu Glu Gly Val Arg Ala Asn Tyr Asp Thr Leu Thr Leu Lys
      115              120              125
Leu Gln Asp Gly Leu Asp Gln Tyr Glu Arg Tyr Ser Glu Gln His Lys
      130              135              140
Glu Ala Ala Phe Phe Lys Glu Leu Val Arg Ser Ile Ser Thr Asn Val
      145              150              155              160
Arg Arg Asn Leu Ala Phe His Thr Leu Ser Gln Glu Val Leu Leu Lys
      165              170              175
Glu Phe Ser Thr Ile Ser
      180

```

```

<210> 93
<211> 255
<212> PRT
<213> Homo sapiens

```

```

      <400> 93
Met Ser Arg Asn Ser Arg Lys Thr Ile Gly Lys Gly Arg Val Asp Tyr
  1              5              10              15
Ile Ile Ile Lys Pro Leu Pro Gly Tyr Ser Cys Asp Met Lys Ser Ser
      20              25              30
Phe Ser Lys Tyr Trp Lys Pro Arg Ile Pro Leu Asp Val Gly His Arg
      35              40              45
Gly Ala Gly Asn Ser Thr Thr Thr Ala Gln Leu Ala Lys Val Gln Glu
      50              55              60
Asn Thr Ile Ala Ser Leu Arg Asn Ala Ala Ser His Gly Ala Ala Phe

```

```

65              70              75              80
Val Glu Phe Asp Val His Leu Ser Lys Asp Phe Val Pro Val Val Tyr
              85              90              95
His Asp Leu Thr Cys Cys Leu Thr Met Lys Lys Lys Phe Asp Ala Asp
              100              105              110
Pro Val Glu Leu Phe Glu Ile Pro Val Lys Glu Leu Thr Phe Asp Gln
              115              120              125
Leu Gln Leu Leu Lys Leu Thr His Val Thr Ala Leu Lys Ser Lys Asp
              130              135              140
Arg Lys Glu Ser Val Val Gln Glu Glu Asn Ser Phe Ser Glu Asn Gln
              145              150              155              160
Pro Phe Pro Ser Leu Lys Met Val Leu Glu Ser Leu Pro Glu Asp Val
              165              170              175
Gly Phe Asn Ile Glu Ile Lys Trp Ile Cys Gln Gln Arg Asp Gly Met
              180              185              190
Trp Asp Gly Asn Leu Ser Thr Tyr Phe Asp Met Asn Leu Phe Leu Asp
              195              200              205
Ile Ile Leu Lys Thr Val Leu Glu Asn Ser Gly Lys Arg Arg Ile Val
              210              215              220
Phe Ser Ser Phe Asp Ala Asp Ile Cys Thr Met Val Arg Gln Lys Gln
              225              230              235              240
Asn Lys Tyr Pro Ile Leu Phe Leu Thr Gln Gly Lys Cys Val Asp
              245              250              255

```

```

<210> 94
<211> 49
<212> PRT
<213> Homo sapiens

```

```

<400> 94
Met Arg Gly Asn Tyr Glu Thr Leu Val Ser Leu Asp Tyr Ala Ile Ser
1              5              10              15
Lys Pro Glu Val Leu Ser Gln Ile Glu Gln Gly Lys Glu Pro Cys Asn
              20              25              30
Trp Arg Arg Pro Gly Pro Lys Ile Pro Asp Val Pro Val Asp Pro Ser
              35              40              45
Pro

```

```

<210> 95
<211> 308
<212> PRT
<213> Homo sapiens

```

```

<400> 95
Met Gly Ser Ser Gly Leu Gly Lys Ala Ala Thr Leu Asp Glu Leu Leu
1              5              10              15
Cys Thr Cys Ile Glu Met Phe Asp Asp Asn Gly Glu Leu Asp Asn Ser
              20              25              30
Tyr Leu Pro Arg Ile Val Leu Leu Met His Arg Trp Tyr Leu Ser Ser
              35              40              45
Thr Glu Leu Ala Glu Lys Leu Leu Cys Met Tyr Arg Asn Ala Thr Gly
              50              55              60
Glu Ser Cys Asn Glu Phe Arg Leu Lys Ile Cys Tyr Phe Met Arg Tyr
              65              70              75              80
Trp Ile Leu Lys Phe Pro Ala Glu Phe Asn Leu Asp Leu Gly Leu Ile
              85              90              95
Arg Met Thr Glu Glu Phe Arg Glu Val Ala Ser Gln Leu Gly Tyr Glu

```

```

      100      105      110
Lys His Val Ser Leu Ile Asp Ile Ser Ser Ile Pro Ser Tyr Asp Trp
      115      120      125
Met Arg Arg Val Thr Gln Arg Lys Lys Val Ser Lys Lys Gly Lys Ala
      130      135      140
Cys Leu Leu Phe Asp His Leu Glu Pro Ile Glu Leu Ala Glu His Leu
      145      150      155      160
Thr Phe Leu Glu His Lys Ser Phe Arg Arg Ile Ser Phe Thr Asp Tyr
      165      170      175
Gln Ser Tyr Val Ile His Gly Cys Leu Glu Asn Asn Pro Thr Leu Glu
      180      185      190
Arg Ser Ile Ala Leu Phe Asn Gly Ile Ser Lys Trp Val Gln Leu Met
      195      200      205
Val Leu Ser Lys Pro Thr Pro Gln Gln Arg Ala Glu Val Ile Thr Lys
      210      215      220
Phe Ile Asn Val Ala Lys Lys Leu Leu Gln Leu Lys Asn Phe Asn Asn
      225      230      235      240
Leu Ile Ala Ile Ala Gly Ser Pro Gln Val Ile Gly Pro Phe Gln Ala
      245      250      255
Ser Lys Gly Pro Ile Pro His Leu Ser Ser Glu Val Tyr Lys Glu Leu
      260      265      270
Glu Cys Glu Met Thr Glu Val Gly Leu Leu Gln Arg Ala Ile Thr Ala
      275      280      285
Ile Thr Ala Ser Pro Leu Pro Thr Ala Met Ala Ser Lys Ser Pro Ser
      290      295      300
Leu Glu Tyr Thr
305

```

```

<210> 96
<211> 217
<212> PRT
<213> Homo sapiens

```

```

      <400> 96
Met Gly Val Pro Val Thr Ser Gln Glu Ser Gly Gln Lys Leu Val Ser
  1      5      10      15
Pro Leu Cys Leu Ala Pro Tyr Phe Arg Leu Leu Lys Leu Cys Val Glu
      20      25      30
Arg Gln His Asn Gly Asn Leu Glu Glu Ile Asp Gly Leu Leu Asn Cys
      35      40      45
Pro Ile Phe Leu Thr Asp Leu Glu Pro Gly Glu Lys Leu Glu Ser Met
      50      55      60
Ser Ala Lys Glu Arg Ser Phe Met Cys Ser Leu Ile Phe Leu Thr Leu
      65      70      75      80
Asn Trp Phe Arg Glu Ile Val Asn Ala Phe Cys Gln Glu Thr Ser Pro
      85      90      95
Glu Met Lys Gly Lys Val Leu Thr Arg Leu Lys His Ile Val Glu Leu
      100      105      110
Gln Ile Ile Leu Glu Lys Tyr Leu Ala Val Thr Pro Asp Tyr Val Pro
      115      120      125
Pro Leu Gly Asn Phe Asp Val Glu Thr Leu Asp Ile Thr Pro His Thr
      130      135      140
Val Thr Ala Ile Ser Ala Lys Ile Arg Lys Lys Gly Lys Ile Val Tyr
      145      150      155      160
Thr Leu Lys Glu Arg Cys Leu Gln Val Val Arg Ser Leu Val Lys Pro
      165      170      175
Glu Asn Tyr Arg Arg Leu Asp Ile Val Arg Ser Leu Tyr Glu Asp Leu
      180      185      190
Glu Asp His Pro Asn Val Gln Lys Asp Leu Glu Arg Leu Thr Gln Glu
      195      200      205
Arg Ile Ala His Gln Arg Met Gly Asp

```

210

215

<210> 97
 <211> 265
 <212> PRT
 <213> Homo sapiens

<400> 97

```

Met Pro Ala Pro Arg Ala Arg Glu Gln Pro Arg Val Pro Gly Glu Arg
 1          5          10          15
Gln Pro Leu Leu Pro Arg Gly Ala Arg Gly Pro Arg Arg Trp Arg Arg
          20          25          30
Ala Ala Gly Ala Ala Val Leu Leu Val Glu Met Leu Glu Arg Ala Ala
 35          40          45
Phe Phe Gly Val Thr Ala Asn Leu Val Leu Tyr Leu Asn Ser Thr Asn
 50          55          60
Phe Asn Trp Thr Gly Glu Gln Ala Thr Arg Ala Ala Leu Val Phe Leu
 65          70          75          80
Gly Ala Ser Tyr Leu Leu Ala Pro Val Gly Gly Trp Leu Ala Asp Val
          85          90          95
Tyr Leu Gly Arg Tyr Arg Ala Val Ala Leu Ser Leu Leu Leu Tyr Leu
          100          105          110
Ala Ala Ser Gly Leu Leu Pro Ala Thr Ala Phe Pro Asp Gly Arg Ser
          115          120          125
Ser Phe Cys Gly Glu Met Pro Ala Ser Pro Leu Gly Pro Ala Cys Pro
 130          135          140
Ser Ala Gly Cys Pro Arg Ser Ser Pro Ser Pro Tyr Cys Ala Pro Val
 145          150          155          160
Leu Tyr Ala Gly Leu Leu Leu Leu Gly Leu Ala Ala Ser Ser Val Arg
          165          170          175
Ser Asn Leu Thr Ser Phe Gly Ala Asp Ala Gly Asp Gly Ser Arg Pro
          180          185          190
Arg Arg His Pro Pro Leu Leu Gln Leu Val Leu Leu Glu His Gln Pro
          195          200          205
Gly Cys Cys Ala Val Ala Ala Gly Gly Gly Val Tyr Ser Ala Glu His
 210          215          220
Gln Leu Pro Ala Gly Leu Gln His Pro Cys Gly Leu Cys Gly Pro Gly
 225          230          235          240
Ile Phe His Leu Pro Leu Cys His Pro Arg Leu His His Gln Ala Pro
          245          250          255
Asp Gly Gln Pro Ser Val Leu Tyr Ala
          260          265

```

<210> 98
 <211> 111
 <212> PRT
 <213> Homo sapiens

<400> 98

```

Met Ile Lys Tyr Asn Glu Gly Arg Ala Glu Gly Leu Ser Leu Ala Val
 1          5          10          15
Pro Gly Cys Cys Gly Gly Gly Arg Leu Ala Thr Gln Thr Val Ala Ala
          20          25          30
Ala Ala Ala Ser Trp Trp Pro Pro Cys Trp Arg Gly Ser Leu Ala Phe
 35          40          45
Ser Val Ala Ala Ser Ala Val Ser Phe Ala Phe Ser Leu Ala Ser Leu
 50          55          60
Ala Val Ser Thr Gly Gly Leu Glu Gly Ala Ser Pro Cys Ser Leu Ala

```

65					70					75				80	
Lys	Ile	Tyr	Ser	Lys	Pro	Phe	Ile	Gly	Leu	Gly	His	Val	Ala	Phe	Glu
				85					90					95	
Pro	Gly	Lys	Thr	Lys	Phe	Leu	Gly	Gln	Leu	Leu	Glu	Thr	Pro	Asn	
			100					105					110		

<210> 99
 <211> 421
 <212> PRT
 <213> Homo sapiens

<400> 99

Met	Ala	Met	Ala	Thr	Cys	Gly	Gly	Lys	Gly	Lys	Gln	Ala	Ala	Pro	Lys
1				5					10					15	
Gly	Arg	Glu	Ala	Phe	Arg	Ser	Gln	Arg	Arg	Glu	Ser	Glu	Gly	Ser	Val
			20					25					30		
Asp	Cys	Pro	Thr	Leu	Glu	Phe	Glu	Tyr	Gly	Asp	Ala	Asp	Gly	His	Ala
		35					40					45			
Ala	Glu	Leu	Ser	Glu	Leu	Tyr	Ser	Tyr	Thr	Glu	Asn	Leu	Glu	Phe	Thr
	50					55					60				
Asn	Asn	Arg	Arg	Cys	Phe	Glu	Glu	Asp	Phe	Lys	Thr	Gln	Val	Gln	Gly
	65				70					75					80
Lys	Glu	Trp	Leu	Glu	Glu	Glu	Glu	Asp	Ala	Gln	Lys	Ala	Tyr	Ile	Met
			85						90					95	
Gly	Leu	Leu	Asp	Arg	Leu	Glu	Val	Val	Ser	Arg	Glu	Arg	Arg	Leu	Lys
			100					105					110		
Ala	Ala	Arg	Ala	Val	Leu	Tyr	Leu	Ala	Gln	Gly	Thr	Phe	Gly	Glu	Cys
		115					120					125			
Asp	Ser	Glu	Val	Asp	Val	Leu	His	Trp	Ser	Arg	Tyr	Asn	Cys	Phe	Leu
	130					135					140				
Leu	Tyr	Gln	Met	Gly	Thr	Phe	Ser	Thr	Phe	Leu	Glu	Leu	Leu	His	Met
	145				150					155				160	
Glu	Ile	Asp	Asn	Ser	Gln	Ala	Cys	Ser	Ser	Ala	Leu	Arg	Lys	Pro	Ala
			165					170					175		
Val	Ser	Ile	Ala	Asp	Ser	Thr	Glu	Leu	Arg	Val	Leu	Leu	Ser	Val	Met
		180					185						190		
Tyr	Leu	Met	Val	Glu	Asn	Ile	Arg	Leu	Glu	Arg	Glu	Thr	Asp	Pro	Cys
	195						200					205			
Gly	Trp	Arg	Thr	Ala	Arg	Glu	Thr	Phe	Arg	Thr	Glu	Leu	Ser	Phe	Ser
	210					215					220				
Met	His	Asn	Glu	Glu	Pro	Phe	Ala	Leu	Leu	Leu	Phe	Ser	Met	Val	Thr
	225				230					235				240	
Lys	Phe	Cys	Ser	Gly	Leu	Ala	Pro	His	Phe	Pro	Ile	Lys	Lys	Val	Leu
			245						250					255	
Leu	Leu	Leu	Trp	Lys	Val	Val	Met	Phe	Thr	Leu	Gly	Gly	Phe	Glu	His
			260					265					270		
Leu	Gln	Thr	Leu	Lys	Val	Gln	Lys	Arg	Ala	Glu	Leu	Gly	Leu	Pro	Pro
	275						280					285			
Leu	Ala	Glu	Asp	Ser	Ile	Gln	Val	Val	Lys	Ser	Met	Arg	Ala	Ala	Ser
	290					295					300				
Pro	Pro	Ser	Tyr	Thr	Leu	Asp	Leu	Gly	Glu	Ser	Gln	Leu	Ala	Pro	Pro
	305				310					315				320	
Pro	Ser	Lys	Leu	Arg	Gly	Arg	Arg	Gly	Ser	Arg	Arg	Gln	Leu	Leu	Thr
			325					330					335		
Lys	Gln	Asp	Ser	Leu	Asp	Ile	Tyr	Asn	Glu	Arg	Asp	Leu	Phe	Lys	Thr
			340					345					350		
Glu	Glu	Pro	Ala	Thr	Glu	Glu	Glu	Glu	Glu	Ser	Ala	Gly	Asp	Gly	Glu
		355					360					365			
Arg	Thr	Leu	Asp	Gly	Glu	Leu	Asp	Leu	Leu	Glu	Gln	Asp	Pro	Leu	Val
	370					375					380				
Pro	Pro	Pro	Pro	Ser	Gln	Ala	Pro	Leu	Ser	Ala	Glu	Arg	Val	Ala	Phe

```

385          390          395          400
Pro Lys Gly Leu Pro Trp Ala Pro Lys Val Arg Gln Lys Gly Thr Leu
          405          410          415
Ser Thr Ser Trp Arg
          420

```

```
<210> 100
<211> 290
<212> PRT
<213> Homo sapiens
```

[illegible]

```
<210> 101
<211> 133
<212> PRT
<213> Homo sapiens
```

<400> 101
Met Pro Pro Arg Asn Leu Pro Gly His Cys Thr Ser Pro Pro Ala Ile


```

      1           5           10           15
Arg Val Pro Pro Val Ile Pro Leu Gly Ser Arg Glu Leu Phe Cys Ser
      20           25           30
Lys Leu Arg Arg Ala Ala Val Phe Pro Pro Ala His Gln Gln Arg Thr
      35           40           45
Leu Arg Pro Cys His Asn Tyr Cys Lys Gly Arg Arg Cys Leu Leu Thr
      50           55           60
His Cys Gly Cys Asp Ala Pro His Leu Pro Arg Ala Pro Pro Pro Leu
      65           70           75           80
Arg Thr Asp Val Gly Asp Ser Thr Pro Phe Arg Glu Lys Pro Val Ser
      85           90           95
Ala Ala Glu Asp Ala Asn Ala Ser Glu Ser Pro Leu Thr Leu Asn His
      100          105          110
Ser Leu Glu Met Gly Val Val Tyr Leu Thr Thr Gly Ala Val Ser Gly
      115          120          125
Asn Ala Asn Tyr His
      130

```

```

<210> 102
<211> 38
<212> PRT
<213> Homo sapiens

```

```

      <400> 102
Met His Arg Ile Trp Ile Glu Asp Thr Thr Trp Lys Phe Ser Asn Phe
      1           5           10           15
Thr Ile Ile Ser Gly Leu Tyr Gly Leu Thr Thr Phe Asn Phe Leu Leu
      20           25           30
Arg Tyr Lys Tyr Phe Pro
      35

```

```

<210> 103
<211> 1130
<212> PRT
<213> Homo sapiens

```

```

      <400> 103
Met Ser Ala Gly Ile Gly Pro Met Ala Trp Trp Pro Ser Thr Thr Gly
      1           5           10           15
Pro Cys Met Met Ser Thr Val Ser Thr Met Ala Lys Pro His Arg Glu
      20           25           30
Cys Pro Gly Cys Phe Val Pro Phe Ala Val Cys Val Val Ser Arg Phe
      35           40           45
Pro Tyr Tyr Asn Ser Leu Lys Asp Cys Leu Ser Cys Leu Leu Ala Leu
      50           55           60
Leu Lys Pro Cys Lys Asp Phe Glu Val Asp Asn His Ile Lys Asp Phe
      65           70           75           80
Ala Ala Lys Leu Ser Leu Ile Pro Ser Pro Pro Pro Gly Pro Leu His
      85           90           95
Leu Val Phe Asn Met Lys Ser Leu Gln Ile Val Leu Pro Ala Arg Ala
      100          105          110
Asp Pro Glu Ser Pro Ile Leu Asp Leu Asp Leu His Leu Pro Leu Leu
      115          120          125
Cys Phe Arg Pro Glu Lys Val Leu Gln Ile Leu Thr Cys Ile Leu Thr
      130          135          140
Glu Gln Arg Ile Val Phe Ser Ser Asp Trp Ala Leu Leu Thr Leu
      145          150          155          160
Val Thr Glu Cys Phe Met Ala Tyr Leu Tyr Pro Leu Gln Trp Gln His

```

				165					170					175	
Pro	Phe	Val	Pro	Ile	Leu	Ser	Asp	Gln	Met	Leu	Asp	Phe	Val	Met	Gly
			180					185					190		
Pro	Thr	Ser	Phe	Leu	Met	Gly	Cys	His	Leu	Asp	His	Phe	Glu	Glu	Val
		195					200					205			
Ser	Lys	Glu	Ala	Asp	Gly	Leu	Val	Leu	Ile	Asn	Ile	Asp	His	Gly	Ser
	210					215					220				
Ile	Thr	Tyr	Ser	Lys	Ser	Thr	Asp	Asp	Asn	Val	Asp	Ile	Pro	Asp	Val
225					230					235				240	
Pro	Leu	Leu	Ala	Ala	Gln	Thr	Phe	Ile	Gln	Arg	Val	Gln	Ser	Leu	Gln
			245						250					255	
Leu	His	His	Glu	Leu	His	Ala	Ala	His	Leu	Leu	Ser	Ser	Thr	Asp	Leu
		260						265					270		
Lys	Glu	Gly	Arg	Ala	His	Arg	Arg	Ser	Trp	Gln	Gln	Lys	Leu	Asn	Cys
	275					280						285			
Gln	Ile	Gln	Gln	Thr	Thr	Leu	Gln	Leu	Leu	Val	Ser	Ile	Phe	Arg	Asp
	290				295						300				
Val	Lys	Asn	His	Leu	Asn	Tyr	Glu	His	Arg	Val	Phe	Asn	Ser	Glu	Glu
305					310					315				320	
Phe	Leu	Lys	Thr	Arg	Ala	Pro	Gly	Asp	His	Gln	Phe	Tyr	Lys	Gln	Val
			325					330						335	
Leu	Asp	Thr	Tyr	Met	Phe	His	Ser	Phe	Leu	Lys	Ala	Arg	Leu	Asn	Arg
	340							345					350		
Arg	Met	Asp	Ala	Phe	Ala	Gln	Met	Asp	Leu	Asp	Thr	Gln	Ser	Glu	Glu
	355					360						365			
Asp	Arg	Ile	Asn	Gly	Met	Leu	Leu	Ser	Pro	Arg	Arg	Pro	Thr	Val	Glu
	370				375						380				
Lys	Arg	Ala	Ser	Arg	Lys	Ser	Ser	His	Leu	His	Val	Thr	His	Arg	Arg
385					390					395				400	
Met	Val	Val	Ser	Met	Pro	Asn	Leu	Gln	Asp	Ile	Ala	Met	Pro	Glu	Leu
			405					410					415		
Ala	Pro	Arg	Asn	Ser	Ser	Leu	Arg	Leu	Thr	Asp	Thr	Ala	Gly	Cys	Arg
			420					425					430		
Gly	Ser	Ser	Ala	Val	Leu	Asn	Val	Thr	Pro	Lys	Ser	Pro	Tyr	Thr	Phe
	435					440						445			
Lys	Ile	Pro	Glu	Ile	His	Phe	Pro	Leu	Glu	Ser	Lys	Cys	Val	Gln	Ala
	450					455					460				
Tyr	His	Ala	His	Phe	Val	Ser	Met	Leu	Ser	Glu	Ala	Met	Cys	Phe	Leu
465					470					475				480	
Ala	Pro	Asp	Asn	Ser	Leu	Leu	Leu	Ala	Arg	Tyr	Leu	Tyr	Leu	Arg	Gly
			485					490						495	
Leu	Val	Tyr	Leu	Met	Gln	Gly	Gln	Leu	Leu	Asn	Ala	Leu	Leu	Asp	Phe
			500					505					510		
Gln	Asn	Leu	Tyr	Lys	Thr	Asp	Ile	Arg	Ile	Phe	Pro	Thr	Asp	Leu	Val
	515					520						525			
Lys	Arg	Thr	Val	Glu	Ser	Met	Ser	Ala	Pro	Glu	Trp	Glu	Gly	Ala	Glu
	530					535					540				
Gln	Ala	Pro	Glu	Leu	Met	Arg	Leu	Ile	Ser	Glu	Ile	Leu	Asp	Lys	Pro
545					550					555				560	
His	Glu	Ala	Ser	Lys	Leu	Asp	Asp	His	Val	Lys	Lys	Phe	Lys	Leu	Pro
			565					570					575		
Lys	Lys	His	Met	Gln	Leu	Gly	Asp	Phe	Met	Lys	Arg	Val	Gln	Glu	Ser
		580						585					590		
Gly	Ile	Val	Lys	Asp	Ala	Ser	Ile	Ile	His	Arg	Leu	Phe	Glu	Ala	Leu
	595					600						605			
Thr	Val	Gly	Gln	Glu	Lys	Gln	Ile	Asp	Pro	Glu	Thr	Phe	Lys	Asp	Phe
	610					615						620			
Tyr	Asn	Cys	Trp	Lys	Glu	Thr	Glu	Ala	Glu	Ala	Gln	Glu	Val	Ser	Leu
625					630					635				640	
Pro	Trp	Leu	Val	Met	Glu	His	Leu	Asp	Lys	Asn	Glu	Cys	Val	Cys	Lys
			645					650						655	
Leu	Ser	Ser	Ser	Val	Lys	Thr	Asn	Leu	Gly	Val	Gly	Lys	Ile	Ala	Met
		660						665					670		
Thr	Gln	Lys	Arg	Leu	Phe	Leu	Leu	Thr	Glu	Gly	Arg	Pro	Gly	Tyr	Leu

```

        675                680                685
Glu Ile Ser Thr Phe Arg Asn Ile Glu Glu Val Arg Arg Thr Thr Thr
        690                695                700
Thr Phe Leu Leu Arg Arg Ile Pro Thr Leu Lys Ile Arg Val Ala Ser
705                710                715                720
Lys Lys Glu Val Phe Glu Ala Asn Leu Lys Thr Glu Cys Asp Leu Trp
        725                730                735
His Leu Met Val Lys Glu Met Trp Ala Gly Lys Lys Leu Ala Asp Asp
        740                745                750
His Lys Asp Pro His Tyr Val Gln Gln Ala Leu Thr Asn Val Leu Leu
755                760                765
Met Asp Ala Val Val Gly Thr Leu Gln Ser Pro Gly Ala Ile Tyr Ala
770                775                780
Ala Ser Lys Leu Ser Tyr Phe Asp Lys Met Ser Asn Glu Met Pro Met
785                790                795                800
Thr Leu Pro Glu Thr Thr Leu Glu Thr Leu Lys His Lys Ile Asn Pro
        805                810                815
Ser Ala Gly Glu Ala Phe Pro Gln Ala Val Asp Val Leu Leu Tyr Thr
        820                825                830
Pro Gly His Leu Asp Pro Ala Glu Lys Val Glu Asp Ala His Pro Lys
835                840                845
Leu Trp Cys Ala Leu Ser Glu Gly Lys Val Thr Val Phe Asn Ala Ser
850                855                860
Ser Trp Thr Ile His Gln His Ser Phe Lys Val Gly Thr Ala Lys Val
865                870                875                880
Asn Cys Met Val Met Ala Asp Gln Asn Gln Val Trp Val Gly Ser Glu
        885                890                895
Asp Ser Val Ile Tyr Ile Ile Asn Val His Ser Met Ser Cys Asn Lys
900                905                910
Gln Leu Thr Ala His Cys Ser Ser Val Thr Asp Leu Ile Val Gln Asp
915                920                925
Gly Gln Glu Ala Pro Ser Asn Val Tyr Ser Cys Ser Met Asp Gly Met
930                935                940
Val Leu Val Trp Asn Val Ser Thr Leu Gln Val Thr Ser Arg Phe Gln
945                950                955                960
Leu Pro Arg Gly Gly Leu Thr Ser Ile Arg Leu His Gly Gly Arg Leu
        965                970                975
Trp Cys Cys Thr Gly Asn Ser Ile Met Val Met Lys Met Asn Gly Ser
980                985                990
Leu His Gln Glu Leu Lys Ile Glu Glu Asn Phe Lys Asp Thr Ser Thr
995                1000                1005
Ser Phe Leu Ala Phe Gln Leu Leu Pro Glu Glu Glu Gln Leu Trp Ala
1010                1015                1020
Ala Cys Ala Gly Arg Ser Glu Val Tyr Ile Trp Ser Leu Lys Asp Leu
1025                1030                1035                1040
Ala Gln Pro Pro Gln Arg Val Pro Leu Glu Asp Cys Ser Glu Ile Asn
        1045                1050                1055
Cys Met Ile Arg Val Lys Lys Gln Val Trp Val Gly Ser Arg Gly Leu
1060                1065                1070
Gly Gln Gly Thr Pro Lys Gly Lys Ile Tyr Val Ile Asp Ala Glu Arg
1075                1080                1085
Lys Thr Val Glu Lys Glu Leu Val Ala His Met Asp Thr Val Arg Thr
1090                1095                1100
Leu Cys Ser Ala Glu Asp Arg Tyr Val Leu Ser Gly Ser Gly Arg Glu
1105                1110                1115                1120
Glu Gly Lys Val Ala Ile Trp Lys Gly Glu
        1125                1130

```

<210> 104

<211> 140

<212> PRT

<213> Homo sapiens

<400> 104
 Met Gly Gln Ala Gln Ser Lys Pro Thr Pro Leu Gly Thr Val Leu Lys
 1 5 10 15
 Asn Phe Lys Lys Gly Ser Asn Gly Asp Tyr Gly Ile Ala Met Thr Pro
 20 25 30
 Gly Lys Leu Lys Ala Leu Cys Glu Ile Asp Trp Pro Ala Leu Glu Val
 35 40 45
 Gly Trp Pro Ser Glu Gly Ser Leu Asp Lys Ser Leu Val Ser Lys Val
 50 55 60
 Trp His Lys Val Thr Glu Phe Pro Val Asn Gln His Gln Leu Glu Asp
 65 70 75 80
 His Ile Leu Ile Lys Gly Trp Lys Glu Arg Lys Leu Glu Pro Ala Trp
 85 90 95
 Glu Gly Pro Tyr Pro Val Leu Leu Thr Thr Lys Thr Ala Val Arg Thr
 100 105 110
 Ala Lys Lys Lys Lys Lys Lys Asp Gly Leu Ile Thr Pro Lys
 115 120 125
 Ser Arg Lys Cys His Pro Leu Gln Ser Arg Gly Pro
 130 135 140

<210> 105
 <211> 562
 <212> PRT
 <213> Homo sapiens

<400> 105
 Met Arg Arg Gly Gly Trp Arg Lys Arg Ala Glu Asn Asp Gly Trp Glu
 1 5 10 15
 Thr Trp Gly Gly Tyr Met Ala Ala Lys Val Gln Lys Leu Glu Glu Gln
 20 25 30
 Phe Arg Ser Asp Ala Ala Met Gln Lys Asp Gly Thr Ser Ser Thr Ile
 35 40 45
 Phe Ser Gly Val Ala Ile Tyr Val Asn Gly Tyr Thr Asp Pro Ser Ala
 50 55 60
 Glu Glu Leu Arg Lys Leu Met Met Leu His Gly Gly Gln Tyr His Val
 65 70 75 80
 Tyr Tyr Ser Arg Ser Lys Thr Thr His Ile Ile Ala Thr Asn Leu Pro
 85 90 95
 Asn Ala Lys Ile Lys Glu Leu Lys Gly Glu Lys Val Ile Arg Pro Glu
 100 105 110
 Trp Ile Val Glu Ser Ile Lys Ala Gly Arg Leu Leu Ser Tyr Ile Pro
 115 120 125
 Tyr Gln Leu Tyr Thr Lys Gln Ser Ser Val Gln Lys Gly Leu Ser Phe
 130 135 140
 Asn Pro Val Cys Arg Pro Glu Asp Pro Leu Pro Gly Pro Ser Asn Ile
 145 150 155 160
 Ala Lys Gln Leu Asn Asn Arg Val Asn His Ile Val Lys Lys Ile Glu
 165 170 175
 Thr Glu Asn Glu Val Lys Val Asn Gly Met Asn Ser Trp Asn Glu Glu
 180 185 190
 Asp Glu Asn Asn Asp Phe Ser Phe Val Asp Leu Glu Gln Thr Ser Pro
 195 200 205
 Gly Arg Lys Gln Asn Gly Ile Pro His Pro Arg Gly Ser Thr Ala Ile
 210 215 220
 Phe Asn Gly His Thr Pro Ser Ser Asn Gly Ala Leu Lys Thr Gln Asp
 225 230 235 240
 Cys Leu Val Pro Met Val Asn Ser Val Ala Ser Arg Leu Ser Pro Ala
 245 250 255
 Phe Ser Gln Glu Glu Asp Lys Ala Glu Lys Ser Ser Thr Asp Phe Arg

```

                260                265                270
Asp Cys Thr Leu Gln Gln Leu Gln Gln Ser Thr Arg Asn Thr Asp Ala
                275                280                285
Leu Arg Asn Pro His Arg Thr Asn Ser Phe Ser Leu Ser Pro Leu His
                290                295                300
Ser Asn Thr Lys Ile Asn Gly Ala His His Ser Thr Val Gln Gly Pro
305                310                315                320
Ser Ser Thr Lys Ser Thr Ser Ser Val Ser Thr Phe Ser Lys Ala Ala
                325                330                335
Pro Ser Val Pro Ser Lys Pro Ser Asp Cys Asn Phe Ile Ser Asn Phe
                340                345                350
Tyr Ser His Ser Arg Leu His His Ile Ser Met Trp Lys Cys Glu Leu
                355                360                365
Thr Glu Phe Val Asn Thr Leu Gln Arg Gln Ser Asn Gly Ile Phe Pro
                370                375                380
Gly Arg Glu Lys Leu Lys Lys Met Lys Thr Gly Arg Ser Ala Leu Val
385                390                395                400
Val Thr Asp Thr Gly Asp Met Ser Val Leu Asn Ser Pro Arg His Gln
                405                410                415
Ser Cys Ile Met His Val Asp Met Asp Cys Phe Phe Val Ser Val Gly
                420                425                430
Ile Arg Asn Arg Pro Asp Leu Lys Gly Lys Pro Val Ala Val Thr Ser
                435                440                445
Asn Arg Gly Thr Gly Arg Ala Pro Leu Arg Pro Gly Ala Asn Pro Gln
                450                455                460
Leu Glu Trp Gln Tyr Tyr Gln Asn Lys Ile Leu Lys Gly Lys Ala Ala
465                470                475                480
Asp Ile Pro Asp Ser Ser Leu Trp Glu Asn Pro Asp Ser Ala Gln Ala
                485                490                495
Asn Gly Ile Asp Ser Val Leu Ser Arg Ala Glu Ile Ala Ser Cys Ser
                500                505                510
Tyr Glu Ala Arg Gln Leu Gly Ile Lys Asn Gly Met Phe Phe Gly His
                515                520                525
Ala Lys Gln Leu Cys Pro Asn Leu Gln Ala Val Pro Tyr Asp Phe His
                530                535                540
Ala Tyr Lys Glu Val Ala Gln Thr Leu Tyr Glu Thr Leu Ala Ser Leu
545                550                555                560
His Ser

```

```

<210> 106
<211> 72
<212> PRT
<213> Homo sapiens

```

```

                <400> 106
Met Glu Lys Ser Ser Gly Pro Trp Asn Lys Thr Ala Pro Val Gln Ala
 1                5                10                15
Pro Pro Ala Pro Val Ile Val Thr Glu Thr Pro Glu Pro Ala Met Thr
                20                25                30
Ser Gly Val Tyr Arg Pro Pro Gly Ala Arg Leu Thr Thr Thr Arg Lys
                35                40                45
Thr Pro Gln Gly Pro Pro Glu Ile Tyr Ser Asp Thr Gln Phe Pro Ser
                50                55                60
Leu Gln Ser Thr Ala Lys His Val
65                70

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<210> 107
<211> 320

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<212> PRT

<213> Homo sapiens

<400> 107

```

Met His Ser Ala Glu Trp Lys Lys Asp Gln Gln Ile Gly Gly Glu Asn
 1          5          10          15
Gly Ala Glu Ile Gln Ile Gln Gly Lys Arg Asn Leu Arg Glu Val Gly
          20          25          30
Gly Glu Asp Gly Val Lys Thr Trp Ala Pro Gly Lys Glu Thr Gln Ser
          35          40          45
Gln Phe Arg Ser Asp Leu Gly Arg Lys Ile Leu Leu Ser Glu Trp Lys
          50          55          60
Ser Gln Lys Gln Met Gly Ser Glu Asn Gly Thr Glu Ile Gln Ala Pro
          65          70          75          80
Val Glu Arg Asn Gln Arg Glu Pro Gly Gly Glu Asp Gly Val Lys Thr
          85          90          95
Gln Arg Pro Lys Arg Glu Asn Glu Asp Gln Leu Asp Ser Glu Ile Gly
          100          105          110
Gly Ser His Ser Pro Gly Arg Arg Asn Trp Glu Leu Ile Gly Lys Asp
          115          120          125
Val Ala Glu Asn Gln Ala Ser Glu Lys Arg Asn Gln Arg Glu Val Gly
          130          135          140
Asn Glu Asp Glu Trp Lys Asn Gln Glu Gln Gly Gly Gly Asn Asp
          145          150          155          160
Glu Glu Ile Gln Ile Gln Gly Lys Arg Asn Leu Arg Gly Thr Thr Ala
          165          170          175
Asp Asp Gly Thr Glu Thr Gln Ala Pro Ala Gly Asp Asp Gln Gly Gln
          180          185          190
Leu Arg Val Glu Ile Ala Glu Glu Ile Gln Val Gln Gly Gln Gly Asn
          195          200          205
Lys Asn Asp Gly Gly Val Glu Asp Val Ala Glu Leu Gln Asp Ile Gly
          210          215          220
Ser Gln Arg Lys Cys Thr Asp Glu Asp Val Gly Glu Pro Arg Ala Pro
          225          230          235          240
Arg Gly Gly Asn Lys Asp Leu Val Arg Gly Glu Asp Ala Val Arg Asp
          245          250          255
Ser Leu Gln Val Asp Cys Ser Gly Ser Glu Arg Pro Thr Gly Arg Lys
          260          265          270
His Ser Leu Pro Trp Pro Pro Ala Phe Thr Gly Tyr Gly Cys Gly Thr
          275          280          285
Arg Glu Gln Glu Gln Ala Val Ala Val Asn Gly Phe Ile Ser Ala Pro
          290          295          300
Cys Pro Glu Met Asn Pro Val Pro His Trp Gly Glu Val Phe Leu Leu
          305          310          315          320

```

<210> 108

<211> 295

<212> PRT

<213> Homo sapiens

<400> 108

```

Met Ser Lys Leu Lys Val Ile Pro Glu Lys Ser Leu Thr Asn Asn Ser
 1          5          10          15
Arg Ile Val Gly Leu Leu Ala Gln Leu Glu Lys Ile Asn Ala Glu Pro
          20          25          30
Ser Glu Ser Asp Thr Ala Arg Tyr Val Thr Ser Lys Ile Leu His Leu
          35          40          45
Ala Gln Ser Gln Glu Lys Thr Arg Arg Glu Met Thr Ala Lys Gly Ser

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```

      50      55      60
Thr Gly Met Glu Ile Leu Leu Ser Thr Leu Glu Asn Thr Lys Asp Leu
65      70      75      80
Gln Thr Thr Leu Asn Ile Leu Ser Ile Leu Val Glu Leu Val Ser Ala
      85      90      95
Gly Gly Gly Arg Arg Val Ser Phe Leu Val Thr Lys Gly Gly Ser Gln
100      105      110
Ile Leu Leu Gln Leu Leu Met Asn Ala Ser Lys Glu Ser Pro Pro His
115      120      125
Glu Asp Leu Met Val Gln Ile His Ser Ile Leu Ala Lys Ile Gly Pro
130      135      140
Lys Asp Lys Lys Phe Gly Val Lys Ala Arg Ile Asn Gly Ala Leu Asn
145      150      155      160
Ile Thr Leu Asn Leu Val Lys Gln Asn Leu Gln Asn His Arg Leu Val
165      170      175
Leu Pro Cys Leu Gln Leu Leu Arg Val Tyr Ser Ala Asn Ser Val Asn
180      185      190
Ser Val Ser Leu Gly Lys Asn Gly Val Val Glu Leu Met Phe Lys Ile
195      200      205
Ile Gly Pro Phe Ser Lys Lys Asn Ser Ser Leu Ile Lys Val Ala Leu
210      215      220
Asp Thr Leu Ala Ala Leu Leu Lys Ser Lys Thr Asn Ala Arg Arg Ala
225      230      235      240
Val Asp Arg Gly Tyr Val Gln Val Leu Leu Thr Ile Tyr Val Asp Trp
245      250      255
His Arg His Asp Asn Arg His Arg Asn Met Leu Ile Arg Lys Gly Ile
260      265      270
Leu Arg Ser Leu Asn Lys Arg Leu Gln Thr Ser Cys Trp Glu Glu Lys
275      280      285
His Leu Leu Met Pro Met Gly
290      295

```

```

<210> 109
<211> 1125
<212> PRT
<213> Homo sapiens

```

```

      <400> 109
Met Asp Pro Phe Thr Glu Lys Leu Leu Glu Arg Thr Arg Ala Arg Arg
1      5      10      15
Glu Asn Leu Gln Arg Lys Met Ala Glu Arg Pro Thr Ala Ala Pro Arg
20      25      30
Ser Met Thr His Ala Lys Arg Ala Arg Gln Pro Leu Ser Glu Ala Ser
35      40      45
Asn Gln Gln Pro Phe Ser Gly Gly Glu Glu Lys Ser Cys Ser Lys Pro
50      55      60
Ser Pro Ser Lys Lys Arg Cys Ser Asp Asn Thr Glu Val Glu Val Ser
65      70      75      80
Asn Leu Glu Asn Lys Gln Pro Val Glu Ser Thr Ser Ala Lys Ser Cys
85      90      95
Ser Pro Ser Pro Val Ser Pro Gln Val Gln Pro Gln Ala Ala Asp Thr
100      105      110
Ile Ser Asp Ser Val Ala Val Pro Ala Ser Leu Leu Gly Met Arg Arg
115      120      125
Gly Leu Asn Ser Arg Leu Glu Ala Thr Ala Ala Ser Ser Val Lys Thr
130      135      140
Arg Met Gln Lys Leu Ala Glu Gln Arg Arg Arg Trp Asp Asn Asp Asp
145      150      155      160
Met Thr Asp Asp Ile Pro Glu Ser Ser Leu Phe Ser Pro Met Pro Ser
165      170      175
Glu Glu Lys Ala Ala Ser Pro Pro Lys Pro Leu Leu Ser Asn Ala Ser

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				180					185					190		
Ala	Thr	Pro	Val	Gly	Arg	Arg	Gly	Arg	Leu	Ala	Asn	Leu	Ala	Ala	Thr	
		195					200					205				
Ile	Cys	Ser	Trp	Glu	Asp	Asp	Val	Asn	His	Ser	Phe	Ala	Lys	Gln	Asn	
	210					215					220					
Ser	Val	Gln	Glu	Gln	Pro	Gly	Thr	Ala	Cys	Leu	Ser	Lys	Phe	Ser	Ser	
225					230					235					240	
Ala	Ser	Gly	Ala	Ser	Ala	Arg	Ile	Asn	Ser	Ser	Ser	Val	Lys	Gln	Glu	
			245						250					255		
Ala	Thr	Phe	Cys	Ser	Gln	Arg	Asp	Gly	Asp	Ala	Ser	Leu	Asn	Lys	Ala	
			260					265					270			
Leu	Ser	Ser	Ser	Ala	Asp	Asp	Ala	Ser	Leu	Val	Asn	Ala	Ser	Ile	Ser	
		275					280					285				
Ser	Ser	Val	Lys	Ala	Thr	Ser	Ser	Pro	Val	Lys	Ser	Thr	Thr	Ser	Ile	
	290					295					300					
Thr	Asp	Ala	Lys	Ser	Cys	Glu	Gly	Gln	Asn	Pro	Glu	Leu	Leu	Pro	Lys	
305					310					315					320	
Thr	Pro	Ile	Ser	Pro	Leu	Lys	Thr	Gly	Val	Ser	Lys	Pro	Ile	Val	Lys	
				325					330					335		
Ser	Thr	Leu	Ser	Gln	Thr	Val	Pro	Ser	Lys	Gly	Glu	Leu	Ser	Arg	Glu	
			340					345				350				
Ile	Cys	Leu	Gln	Ser	Gln	Ser	Lys	Asp	Lys	Ser	Thr	Thr	Pro	Gly	Gly	
		355					360					365				
Thr	Gly	Ile	Lys	Pro	Phe	Leu	Glu	Arg	Phe	Gly	Glu	Arg	Cys	Gln	Glu	
		370				375					380					
His	Ser	Lys	Glu	Ser	Pro	Ala	Arg	Ser	Thr	Pro	His	Arg	Thr	Pro	Ile	
385					390					395				400		
Ile	Thr	Pro	Asn	Thr	Lys	Ala	Ile	Gln	Glu	Arg	Leu	Phe	Lys	Gln	Asp	
				405					410					415		
Thr	Ser	Ser	Ser	Thr	Thr	His	Leu	Ala	Gln	Gln	Leu	Lys	Gln	Glu	Arg	
			420					425					430			
Gln	Lys	Glu	Leu	Ala	Cys	Leu	Arg	Gly	Arg	Phe	Asp	Lys	Gly	Asn	Ile	
		435					440					445				
Trp	Ser	Ala	Glu	Lys	Gly	Gly	Asn	Ser	Lys	Ser	Lys	Gln	Leu	Glu	Thr	
		450				455					460					
Lys	Gln	Glu	Thr	His	Cys	Gln	Ser	Thr	Pro	Leu	Lys	Lys	His	Gln	Gly	
465					470					475				480		
Val	Ser	Lys	Thr	Gln	Ser	Leu	Pro	Val	Thr	Glu	Lys	Val	Thr	Glu	Asn	
				485					490					495		
Gln	Ile	Pro	Ala	Lys	Asn	Ser	Ser	Thr	Glu	Pro	Lys	Gly	Phe	Thr	Glu	
			500					505					510			
Cys	Glu	Met	Thr	Lys	Ser	Ser	Pro	Leu	Lys	Ile	Thr	Leu	Phe	Leu	Glu	
		515					520									

690	695	700
Asp Glu Lys Asn Asn Ala Phe Pro Cys Gln Val Asn Ile Lys Gln Lys		
705	710	715
Met Gln Glu Leu Asn Asn Glu Ile Asn Met Gln Gln Thr Val Ile Tyr		720
	725	730
Gln Ala Ser Gln Ala Leu Asn Cys Cys Val Asp Glu Glu His Gly Lys		735
	740	745
Gly Ser Leu Glu Glu Ala Glu Ala Glu Arg Leu Leu Leu Ile Ala Thr		750
	755	760
Gly Lys Arg Thr Leu Leu Ile Asp Glu Leu Asn Lys Leu Lys Asn Glu		765
	770	775
Gly Pro Gln Arg Lys Asn Lys Ala Ser Pro Gln Ser Glu Phe Met Pro		780
785	790	795
Ser Lys Gly Ser Val Thr Leu Ser Glu Ile Arg Leu Pro Leu Lys Ala		800
	805	810
Asp Phe Val Cys Ser Thr Val Gln Lys Pro Asp Ala Ala Asn Tyr Tyr		815
	820	825
Tyr Leu Ile Ile Leu Lys Ala Gly Ala Glu Asn Met Val Ala Thr Pro		830
	835	840
Leu Ala Ser Thr Ser Asn Ser Leu Asn Gly Asp Ala Leu Thr Phe Thr		845
	850	855
Thr Thr Phe Thr Leu Gln Asp Val Ser Asn Asp Phe Glu Ile Asn Ile		860
865	870	875
Glu Val Tyr Ser Leu Val Gln Lys Lys Asp Pro Ser Gly Leu Asp Lys		880
	885	890
Lys Lys Lys Thr Ser Lys Ser Lys Ala Ile Thr Pro Lys Arg Leu Leu		895
	900	905
Thr Ser Ile Thr Thr Lys Ser Asn Ile His Ser Ser Val Met Ala Ser		910
	915	920
Pro Gly Gly Leu Ser Ala Val Arg Thr Ser Asn Phe Ala Leu Val Gly		925
	930	935
Ser Tyr Thr Leu Ser Leu Ser Ser Val Gly Asn Thr Lys Phe Val Leu		940
945	950	955
Asp Lys Val Pro Phe Leu Ser Ser Leu Glu Gly His Ile Tyr Leu Lys		960
	965	970
Ile Lys Cys Gln Val Asn Ser Ser Val Glu Glu Arg Gly Phe Leu Thr		975
	980	985
Ile Phe Glu Asp Val Ser Gly Phe Gly Ala Trp His Arg Arg Trp Cys		990
	995	1000
Val Leu Ser Gly Asn Cys Ile Ser Tyr Trp Thr Tyr Pro Asp Asp Glu		1005
	1010	1015
Lys Arg Lys Asn Pro Ile Gly Arg Ile Asn Leu Ala Asn Cys Thr Ser		1020
1025	1030	1035
Arg Gln Ile Glu Pro Ala Asn Arg Glu Phe Cys Ala Arg Arg Asn Thr		1040
	1045	1050
Phe Glu Leu Ile Thr Val Arg Pro Gln Arg Glu Asp Asp Arg Glu Thr		1055
	1060	1065
Leu Val Ser Gln Cys Arg Asp Thr Leu Cys Val Thr Lys Asn Trp Leu		1070
	1075	1080
Ser Ala Asp Thr Lys Glu Glu Arg Asp Leu Trp Met Gln Lys Leu Asn		1085
	1090	1095
Gln Val Leu Val Asp Ile Arg Leu Trp Gln Pro Asp Ala Cys Tyr Lys		1100
1105	1110	1115
Pro Ile Gly Lys Pro		1120
	1125	

<210> 110

<211> 226

<212> PRT

<213> Homo sapiens

<400> 110
 Met Cys His Pro Gln Arg Cys Pro Gln Thr Val Ile Pro Glu Gly Glu
 1 5 10 15
 Cys Cys Pro Val Cys Ser Ala Thr Val Ser Tyr Ser Leu Leu Ser Gly
 20 25 30
 Ile Ala Leu Asn Asp Arg Asn Glu Phe Ser Gly Asp Ser Ser Glu Gln
 35 40 45
 Arg Glu Pro Thr Asn Leu Leu His Lys Gln Leu Pro Pro Pro Gln Val
 50 55 60
 Gly Met Asp Arg Ile Val Arg Lys Glu Ala Leu Gln Ser Glu Glu Asp
 65 70 75 80
 Glu Glu Val Lys Glu Glu Asp Thr Glu Gln Lys Arg Glu Thr Pro Glu
 85 90 95
 Ser Arg Asn Gln Gly Gln Leu Tyr Ser Glu Gly Asp Ser Arg Gly Gly
 100 105 110
 Asp Arg Lys Gln Arg Pro Gly Glu Glu Arg Arg Leu Ala His Gln Gln
 115 120 125
 Gln Arg Gln Gly Arg Glu Glu Glu Asp Glu Glu Glu Gly Glu
 130 135 140
 Glu Gly Glu Glu Asp Glu Glu Asp Glu Glu Asp Pro Val Arg Gly Asp
 145 150 155 160
 Met Phe Arg Met Pro Ser Arg Ser Pro Leu Pro Ala Pro Pro Arg Gly
 165 170 175
 Thr Leu Arg Leu Pro Ser Gly Cys Ser Leu Ser Tyr Arg Thr Ile Ser
 180 185 190
 Cys Ile Asn Ala Lys Leu Thr Ala Asn Thr Thr Ala Asp Ser Thr Thr
 195 200 205
 Asp Asn Lys Ser Gly Ser Leu Thr Trp Gln Tyr Pro Ser Ala Ser Ile
 210 215 220
 Ser Arg
 225

<210> 111
 <211> 100
 <212> PRT
 <213> Homo sapiens

<400> 111
 Met Tyr Arg Ala Ser Glu Ser Ala Lys Trp Ser Leu Gly Gly Gly Glu
 1 5 10 15
 Glu Gln Gln Lys Pro Trp Leu Arg Leu Thr His Gln Gly Leu Pro Cys
 20 25 30
 Pro Pro Glu Glu Val Ser Gly Ile Gln Thr Phe Ser Ser Asp Pro Cys
 35 40 45
 Leu Pro Gly Gly Leu Glu Ala His Ala Leu Lys Gln Val Ser Ala Ile
 50 55 60
 Asn Ser Arg Thr Arg Pro Lys Asp Lys Ile Leu Glu Gln Lys His Arg
 65 70 75 80
 Pro Ser Leu Asp Gln Gly Lys Gln Leu Ser Met Lys Lys Glu Lys Ile
 85 90 95
 Pro Val Gly Gly
 100

<210> 112
 <211> 155
 <212> PRT
 <213> Homo sapiens

<400> 112

```

Met Ser Arg Trp Gly Ala Ala Val Gly Gln Gly Ala Leu Arg Glu Glu
 1          5          10          15
His Phe Ala His Ala His Ile Thr Glu Arg Thr Arg Arg Val Arg Glu
          20          25          30
Gly Arg Arg Lys Arg Arg Ser Ser Leu Leu Thr Thr Ser Pro Thr Ser
          35          40          45
Ala Asn Ala Gln Ala His Phe Leu Lys Leu Lys Val Ser Ile Asp Lys
          50          55          60
Gly Pro Gln Asn Arg Ala Gly Ala Ile Val Pro Trp Phe Ala Lys Met
65          70          75          80
Ser Phe Pro Lys Tyr Lys Pro Cys Glu Pro Ala His Ser Ala Val Arg
          85          90          95
Pro Ser Thr Gln Pro Asn Thr Thr Tyr Leu Arg Lys Pro Gly Gly Arg
          100          105          110
Lys Pro Glu Arg Leu Ala His Arg Ser Pro Ala Ala Asn Glu Ser Thr
          115          120          125
Leu Leu Gln Tyr Asn Asp Pro Asn Thr Pro Arg Ala His Arg Lys Ser
          130          135          140
Val Pro Cys Phe Val Gly Pro Met Gln Glu Gln
145          150          155

```

<210> 113

<211> 194

<212> PRT

<213> Homo sapiens

<400> 113

```

Met Gln Phe Arg Arg Ala Pro Phe Met Tyr Ser Val Arg Met Glu Leu
 1          5          10          15
Ala Gly Val Pro Cys Glu Leu Thr Cys Phe Leu Pro Gln Gly Ile Cys
          20          25          30
Leu Leu Met Val Pro Ala Val Lys Asn Gln Ala Ser Gly Ser Ala Arg
          35          40          45
Gly Ala Thr Lys Val Arg Arg Lys Cys Gln Ala Gly Cys Gln Asn Glu
          50          55          60
His Leu Gly Glu Leu Asp Asp Gly Thr Asp Gly Lys Asn Gln Leu Asn
65          70          75          80
Ile Arg Glu Asn Gly Gly Arg Gly Gln Asn Cys Glu Gln Glu Leu Glu
          85          90          95
Glu Ser Val Ala Glu Lys Asp Leu Ser Gln Thr Ser Arg Asp Leu Glu
          100          105          110
Lys Met Met Ser Lys His Ile Phe Leu Lys Pro Met Leu Ser Ile Ser
          115          120          125
Asp Leu Val Asn Phe Leu Met Gln Val Ser Lys Val Leu Val Lys Thr
          130          135          140
Ala Glu Gly Ile Val Leu Gln Gln Leu Pro Leu Ala Phe Pro Ala Leu
145          150          155          160
His Phe His Ala Tyr Gly Asn Leu Phe Pro Val Cys Ser Phe Lys His
          165          170          175
Tyr Ile Tyr Met Ile Asp His Pro Ile Phe Ile Ser Ile Pro Asp Phe
          180          185          190
Leu Thr

```

<210> 114

<211> 814

<212> PRT

<213> Homo sapiens

<400> 114
Met Glu Gly Glu Pro Thr Leu Phe Lys Ile Cys Arg Lys His Ser Glu
1 5 10 15
Ser Lys Gly Lys Leu Val Ser Lys Tyr Phe Ser Met Glu Cys Leu Ile
20 25 30
Val Glu Val Val Phe Ile Thr Gly Glu Arg Ile Ala Ile Ser Lys Ser
35 40 45
Val Ser Leu His His Glu Asn Ala Glu Tyr Gly Ile Arg Arg Thr Glu
50 55 60
Ser Leu Asp Phe Lys Phe Gly Arg Arg Ser Asn Arg Ala Asp Glu Leu
65 70 75 80
Thr Gly Gly Glu Tyr Ser Val Ala Phe Ser Ser Leu Glu Arg Asn Ala
85 90 95
Ala Thr Ala Gly Asn Arg Gly Leu Ala Phe Pro Ser Arg His Ile Asn
100 105 110
Ile Gly Arg Ser Gln Ser Trp Asp Ala Ala Gly Trp Tyr Glu Gly Pro
115 120 125
Trp Glu Asn Ala Glu Ser Leu Arg Pro Leu Gly Arg Arg Ser Ser Leu
130 135 140
Thr Tyr Gly Thr Ala Glu Gly Thr Trp Phe Glu Pro Asn His Arg Pro
145 150 155 160
Gln Asp Ala Ala Leu Pro Val Ala Ala Glu Pro Tyr Leu Tyr Arg Glu
165 170 175
Ala Val Tyr Asn Ser Val Ala Ala Arg Lys Gly Ser Thr Pro Asp Phe
180 185 190
Thr Phe Tyr Asp Ser Arg Gln Ala Val Met Ser Gly Arg Ser Pro Leu
195 200 205
Leu Pro Arg Glu Tyr Tyr Ser Asp Pro Ser Gly Ala Ala Arg Val Pro
210 215 220
Lys Glu Pro Pro Leu Tyr Arg Asp Pro Gly Val Ser Arg Pro Val Pro
225 230 235 240
Ser Tyr Gly Val Leu Gly Ser Arg Thr Ser Trp Asp Pro Met Gln Gly
245 250 255
Arg Ser Pro Ala Leu Gln Asp Ala Gly His Leu Tyr Arg Asp Pro Gly
260 265 270
Gly Lys Met Ile Pro Gln Gly Arg Gln Thr Gln Ser Arg Ala Ala Ser
275 280 285
Pro Gly Arg Tyr Gly Arg Glu Gln Pro Asp Thr Arg Tyr Gly Ala Glu
290 295 300
Val Pro Ala Tyr Pro Leu Ser Gln Val Phe Ser Asp Ile Ser Glu Arg
305 310 315 320
Pro Ile Asp Pro Ala Pro Ala Arg Gln Val Ala Pro Thr Cys Leu Val
325 330 335
Val Asp Pro Ser Ser Ala Ala Ala Pro Glu Gly Ser Thr Gly Val Ala
340 345 350
Pro Gly Ala Leu Asn Arg Gly Tyr Gly Pro Ala Arg Glu Ser Ile Pro
355 360 365
Ser Lys Met Ala Tyr Glu Thr Tyr Glu Ala Asp Leu Ser Thr Phe Gln
370 375 380
Gly Pro Gly Gly Lys Arg Thr Val Leu Pro Glu Phe Leu Ala Phe Leu
385 390 395 400
Arg Ala Glu Gly Leu Ala Glu Ala Thr Leu Gly Ala Leu Leu Gln Gln
405 410 415
Gly Phe Asp Ser Pro Ala Val Leu Ala Thr Leu Glu Asp Ala Asp Ile
420 425 430
Lys Ser Val Ala Pro Asn Leu Gly Gln Ala Arg Val Leu Ser Arg Leu
435 440 445
Ala Asn Ser Cys Arg Thr Glu Met Gln Leu Arg Arg Gln Asp Arg Gly
450 455 460
Gly Pro Leu Pro Arg Ala Arg Ser Ser Ser Phe Ser His Arg Ser Glu
465 470 475 480
Leu Leu His Gly Asp Leu Ala Ser Leu Gly Ala Ala Ala Pro Leu Gln

					485					490					495	
Thr	Ala	Ser	Pro	Arg	Ala	Gly	Asp	Pro	Ala	Arg	Arg	Pro	Ser	Ser	Ala	
			500					505						510		
Pro	Ser	Gln	His	Leu	Leu	Glu	Thr	Ala	Ala	Thr	Tyr	Ser	Ala	Pro	Gly	
		515					520					525				
Val	Gly	Thr	His	Ala	Pro	His	Phe	Pro	Ser	Asn	Ser	Gly	Tyr	Ser	Ser	
	530					535					540					
Pro	Thr	Pro	Cys	Ala	Leu	Thr	Ala	Arg	Leu	Ser	Pro	Thr	Tyr	Pro	Leu	
545				550					555						560	
Gln	Ala	Gly	Val	Ala	Leu	Thr	Asn	Pro	Gly	Pro	Ser	Asn	Pro	Leu	His	
			565						570					575		
Pro	Gly	Pro	Arg	Thr	Ala	Tyr	Ser	Thr	Ala	Tyr	Thr	Val	Pro	Met	Glu	
			580					585					590			
Leu	Leu	Lys	Arg	Glu	Arg	Asn	Val	Ala	Ala	Ser	Pro	Leu	Pro	Ser	Pro	
		595					600					605				
His	Gly	Ser	Pro	Gln	Val	Leu	Arg	Lys	Pro	Gly	Ala	Pro	Leu	Gly	Pro	
	610					615					620					
Ser	Thr	Leu	Pro	Pro	Ala	Ser	Gln	Ser	Leu	His	Thr	Pro	His	Ser	Pro	
625				630						635					640	
Tyr	Gln	Lys	Val	Ala	Arg	Arg	Thr	Gly	Ala	Pro	Ile	Ile	Val	Ser	Thr	
			645						650					655		
Met	Leu	Ala	Pro	Glu	Pro	Ile	Gln	Phe	Ala	Gly	Gln	Ala	Val	Gln	Ser	
			660					665					670			
Asp	Asn	Val	Arg	Lys	Ala	Tyr	Ala	Ala	Gly	Thr	Pro	Val	Arg	Pro	Thr	
		675					680					685				
Ser	Pro	Gly	Asp	Thr	Asp	Lys	Trp	Gly	Leu	Gln	Ala	Arg	Val	Ser	Gly	
	690					695					700					
Ser	Thr	Trp	Gln	Val	Val	Gly	Ser	Ala	Val	Ala	Leu	Arg	Leu	Thr	Trp	
705				710						715					720	
Pro	Ala	Met	Ala	Gln	Val	Ala	Glu	Pro	Ser	Gly	Gly	Gly	Cys	Glu	Pro	
			725						730					735		
Ala	Ile	Ser	Pro	Cys	His	Val	Leu	Ser	Pro	Glu	Pro	Cys	Leu	His	Gln	
			740					745					750			
Met	Gln	Gln	Gly	Ser	Ser	Glu	Thr	Thr	Asn	Glu	Trp	Gly	Cys	Gly	His	
		755						760				765				
Phe	His	Ile	Phe	Val	Phe	Thr	Lys	Tyr	Ser	Gln	Ala	Cys	Ser	Leu	His	
	770					775					780					
Arg	Ala	Gln	Leu	Arg	Thr	His	Pro	Val	Thr	Arg	Ala	Gly	His	Ser	His	
785				790						795					800	
Gly	Phe	Phe	Ser	Cys	Gly	Leu	Gly	Phe	Gln	Gln	Leu	Glu	Val			
				805					810							

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<210> 115
<211> 241
<212> PRT
<213> Homo sapiens
```

<400> 115															
Met	Val	Ser	Lys	Arg	Arg	Leu	Ser	Lys	Ser	Glu	Asp	Lys	Glu	Ser	Leu
1				5					10					15	
Thr	Glu	Asp	Ala	Ser	Lys	Thr	Arg	Lys	Gln	Pro	Leu	Ser	Lys	Lys	Thr
			20					25					30		
Lys	Lys	Ser	His	Ile	Ala	Asn	Glu	Val	Glu	Glu	Asn	Asp	Ser	Ile	Phe
		35					40				45				
Val	Lys	Leu	Leu	Lys	Ile	Ser	Gly	Ile	Ile	Leu	Lys	Thr	Gly	Glu	Ser
	50					55					60				
Gln	Asn	Gln	Leu	Ala	Val	Asp	Gln	Ile	Ala	Phe	Gln	Lys	Lys	Leu	Phe
65					70					75					80
Gln	Thr	Leu	Arg	Arg	His	Pro	Ser	Tyr	Pro	Thr	Ile	Ile	Glu	Glu	Phe
				85					90					95	
Val	Ser	Gly	Leu	Glu	Ser	Tyr	Ile	Glu	Asp	Glu	Asp	Ser	Leu	Arg	Asn

```

      100      105      110
Cys Leu Leu Ser Cys Glu Arg Leu Gln Asp Glu Glu Ala Ser Met Gly
      115      120      125
Ala Ser Tyr Ser Lys Ser Leu Ile Lys Leu Leu Leu Gly Ile Asp Ile
      130      135      140
Leu Gln Pro Ala Ile Ile Lys Thr Leu Phe Glu Lys Leu Pro Glu Tyr
145      150      155      160
Phe Phe Glu Asn Lys Asn Ser Asp Glu Ile Asn Ile Pro Arg Leu Ile
      165      170      175
Val Ser Gln Leu Lys Trp Leu Asp Arg Val Val Asp Gly Lys Asp Leu
      180      185      190
Thr Thr Lys Ile Met Gln Leu Ile Ser Ile Ala Pro Glu Asn Leu Gln
      195      200      205
His Asp Ile Ile Thr Ser Leu Pro Glu Ile Leu Gly Asp Ser Gln His
      210      215      220
Ala Asp Val Gly Lys Glu Leu Arg Trp Ile Asn Pro Leu Ser Ser Ser
225      230      235      240
Lys

```

<210> 116
 <211> 396
 <212> PRT
 <213> Homo sapiens

```

      <400> 116
Met Val Glu Arg Arg Pro Tyr Leu Asp Ala Arg Pro Arg Asn Ser His
 1      5      10      15
Thr Asn His Arg Gly Pro Val Asp Gly Glu Leu Pro Pro Arg Ala Arg
      20      25      30
Asn Gln Ala Asn Asn Pro Pro Ala Asn Ala Leu Arg Gly Gly Ala Ser
      35      40      45
His Pro Gly Ser Asp Pro Arg Ala Asn Asn His Pro Ala Ala Tyr Cys
      50      55      60
Gln Arg Glu Glu Arg Phe Arg Ala Met Gly Trp Asn Pro His Gln Gly
      65      70      75      80
Ser Glu Glu Gln Glu Trp His Val Cys Asp Glu Ala Arg Asp Gln Arg
      85      90      95
His Cys Gln Gly Asn Asp Thr Arg Trp Arg Asn Gly Asn Gln Asp Cys
      100      105      110
Arg Asn Arg Arg Pro Pro Trp Ser Asn Asp Asn Phe Gln Gln Trp Arg
      115      120      125
Thr Pro His Gln Lys Pro Thr Glu Gln Pro Gln Gln Ala Lys Lys Leu
      130      135      140
Gly Tyr Lys Phe Leu Glu Ser Leu Leu Gln Lys Asp Pro Ser Glu Val
145      150      155      160
Val Ile Thr Leu Ala Thr Ser Leu Gly Leu Lys Glu Leu Leu Ser His
      165      170      175
Ser Ser Met Lys Ser Asn Phe Leu Glu Leu Ile Cys Gln Val Leu Arg
      180      185      190
Lys Ala Cys Ser Ser Lys Met Asp Arg Gln Ser Val Leu His Val Leu
      195      200      205
Gly Ile Leu Lys Asn Ser Lys Phe Leu Lys Val Cys Leu Pro Ala Tyr
      210      215      220
Val Val Gly Met Ile Thr Glu Pro Ile Pro Asp Ile Arg Asn Gln Tyr
225      230      235      240
Pro Glu His Ile Ser Asn Ile Ile Ser Leu Gln Asp Leu Val Ser
      245      250      255
Val Phe Pro Ala Ser Ser Val Gln Glu Thr Ser Met Leu Val Ser Leu
      260      265      270
Leu Pro Thr Ser Leu Asn Ala Leu Arg Ala Ser Gly Val Asp Ile Glu

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      275      280      285
Glu Glu Thr Glu Lys Asn Leu Glu Lys Val Gln Thr Ile Ile Glu His
 290      295      300
Leu Gln Glu Lys Arg Arg Glu Gly Thr Leu Arg Val Asp Thr Tyr Thr
305      310      315
Leu Val Gln Ala Glu Glu Arg Gly Arg Met Leu Arg Ala Thr Leu Thr
      325      330      335
Met Pro Arg Tyr Pro Thr Tyr Thr Glu Ala His Leu Gly Glu Glu Ala
      340      345      350
Leu Pro Ser Pro Gln Tyr His Phe Trp Lys Ile Arg Gln His Cys Tyr
      355      360      365
Leu Ser Gly Tyr Pro Leu Pro Ala Ser Gly Arg Arg Phe Arg Gln Thr
      370      375      380
Phe Thr Gly Arg Tyr Phe Gly Thr Ser Pro Lys Leu
385      390      395

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<210> 117
<211> 153
<212> PRT
<213> Homo sapiens

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      <400> 117
Met Gly Trp Leu Phe Leu Lys Val Leu Val Ala Gly Glu Ser Phe Ser
 1      5      10      15
Gly Leu Leu Tyr Pro Leu Val Asp Phe Cys Ile Ser Gly Lys Thr Arg
      20      25      30
Gly Gln Lys Pro Asn Phe Val Ile Ile Leu Ala Asp Asp Met Gly Trp
      35      40      45
Gly Asp Leu Gly Ala Asn Trp Ala Glu Thr Lys Asp Thr Ala Asn Leu
      50      55      60
Asp Asn Met Ala Ser Glu Gly Met Arg Phe Val Asp Phe His Ala Ala
      65      70      75      80
Ala Ser Thr Cys Ser Pro Ser Arg Ala Ser Leu Leu Thr Gly Arg Leu
      85      90      95
Gly Leu Arg Asn Gly Val Thr Arg Asn Phe Ala Val Thr Ser Val Gly
      100      105      110
Gly Leu Pro Leu Asn Glu Thr Thr Leu Ala Glu Val Leu Gln Gln Ala
      115      120      125
Gly Tyr Val Thr Gly Ile Ile Gly Lys Trp His Leu Gly His His Gly
      130      135      140
Ser Tyr Gln Pro Arg Val Pro Trp Ser
145      150

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<210> 118
<211> 169
<212> PRT
<213> Homo sapiens

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      <400> 118
Met Pro Pro Asn Asn Cys Tyr Val Asn Phe Glu Arg Phe Ala Cys Val
 1      5      10      15
Val Glu Asp Val Ala Arg Val Asp Leu Gly Cys Arg Ala Leu Val Glu
      20      25      30
Ala His Asp Thr Ile Gln Asp Asp Val Glu Ala Leu Val Ser Ile Phe
      35      40      45
Asn Glu Lys Glu Ala Trp Tyr Arg Glu Glu Asn Glu Ser Ala Arg His
      50      55      60
Asp Leu Ser Gln Leu Arg Tyr Glu Phe Arg Lys Val Glu Ser Leu Lys

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      65              70              75              80
Lys Leu Leu Arg Glu Asp Ile Gln Ala Thr Gly Cys Ser Leu Gly Ser
      85              90              95
Met Ala Arg Lys Leu Asp His Leu Gln Ala Gln Phe Glu Ile Leu Arg
      100              105              110
Gln Glu Leu Ser Ala Asp Leu Gln Trp Ile Gln Glu Leu Val Gly Ser
      115              120              125
Phe Gln Leu Glu Ser Gly Ser Ser Glu Gly Leu Gly Ser Thr Phe Tyr
      130              135              140
Gln Asp Thr Ser Glu Ser Leu Ser Glu Leu Leu Ser Arg Ser Cys Thr
      145              150              155              160
Glu Glu Phe Leu Ala Gly Trp Lys Leu
      165

```

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<210> 119
<211> 51
<212> PRT
<213> Homo sapiens

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      <400> 119
Met Val Pro Val Phe Ser Val Glu Lys Asp Gly Glu Glu Leu Gly Ser
      1              5              10              15
Phe Arg Pro Arg Trp Ala Asp Trp Leu Thr Gly Leu Leu Glu Trp Val
      20              25              30
Ser Val Glu Ser Leu Ser Ile Tyr Cys Ile Ser Gln Pro Val Tyr Met
      35              40              45
Trp Val Glu
      50

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<210> 120
<211> 169
<212> PRT
<213> Homo sapiens

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```

      <400> 120
Met Gly Ser Lys Gly Arg Ser Leu Asp Ala Arg Ser Arg Gly Gly Arg
      1              5              10              15
Thr Ser Met Arg Lys Pro Leu Ala Glu Asn Gly Arg Ser Ser Ala Ala
      20              25              30
Ser Gln Pro Gln Leu Pro Gly Arg Cys Ser Arg Asp Ile Gly Gly Val
      35              40              45
Asn Ile Gln Lys Cys Asp Cys Leu Thr Gln Pro Arg Ala Leu Ala Ile
      50              55              60
Ile Lys Arg Cys Ser Asp Gly Ala Val Gln Glu Cys Asp Ala Gly Glu
      65              70              75              80
Leu Glu Gln Gln Ser His Ile Ser Thr Ser Arg Pro Thr Ala Val Ser
      85              90              95
His Thr Leu Glu Pro Ser Phe Ala Gln Ser His Met His Asp Trp Asp
      100              105              110
Arg Gly Phe Arg Pro Leu Pro Thr Pro His Ala Gly Ser Val Pro Asp
      115              120              125
Ala Gln Val Pro His Trp Gly Ala Leu Ser Arg Leu Leu His Thr Leu
      130              135              140
Arg Ser Cys Pro Pro Gln Glu Arg Leu Arg Ala Ser Ser Val Lys Trp
      145              150              155              160
Asn Ser Lys Gln Pro Pro Gly His Ser
      165

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<210> 121
 <211> 428
 <212> PRT
 <213> Homo sapiens

<400> 121
 Met Ser Val Asp Tyr Gln Ala Ser Phe Val Gly His Pro Pro Gly Ser
 1 5 10 15
 Ala Tyr Pro Lys Leu Asn Phe Val Glu Asp Ser Lys Val Val Leu Gly
 20 25 30
 Asp Ser Lys Glu Gly Ala Phe Ala Tyr Val His His Leu Thr Leu Tyr
 35 40 45
 Asp Leu Glu Ala Arg Gly Phe Val Arg Pro Phe Cys Met Ala Tyr Ile
 50 55 60
 Ser Ala Asp Gln His Lys Ile Met Gln Gln Phe Gln Glu Leu Ser Ala
 65 70 75 80
 Glu Phe Ser Arg Ala Ser Glu Cys Leu Lys Thr Gly Asn Arg Lys Ala
 85 90 95
 Phe Ala Gly Glu Leu Glu Lys Lys Leu Lys Asp Leu Asp Tyr Thr Arg
 100 105 110
 Thr Val Leu His Thr Glu Thr Glu Ile Gln Lys Lys Ala Asn Asp Lys
 115 120 125
 Gly Phe Tyr Ser Ser Gln Ala Ile Glu Lys Ala Asn Glu Leu Ala Ser
 130 135 140
 Val Glu Lys Ser Ile Ile Glu His Gln Asp Leu Leu Lys Gln Ile Arg
 145 150 155 160
 Ser Tyr Pro His Arg Lys Leu Lys Gly His Asp Leu Cys Pro Gly Glu
 165 170 175
 Met Glu His Ile Gln Asp Gln Ala Ser Gln Ala Ser Thr Thr Ser Asn
 180 185 190
 Pro Asp Glu Ser Ala Asp Thr Asp Leu Tyr Thr Cys Arg Pro Ala Tyr
 195 200 205
 Thr Pro Lys Leu Ile Lys Ala Lys Ser Thr Lys Cys Phe Asp Lys Lys
 210 215 220
 Leu Lys Thr Leu Glu Glu Leu Cys Asp Thr Glu Tyr Phe Thr Gln Thr
 225 230 235 240
 Leu Ala Gln Leu Ser His Ile Glu His Met Phe Arg Gly Asp Leu Cys
 245 250 255
 Tyr Leu Leu Thr Ser Gln Ile Asp Arg Ala Leu Leu Lys Gln Gln His
 260 265 270
 Ile Thr Asn Phe Leu Phe Glu Asp Phe Val Glu Val Asp Asp Arg Met
 275 280 285
 Val Glu Lys Gln Glu Ser Ile Pro Ser Lys Pro Ser Gln Asp Arg Pro
 290 295 300
 Pro Ser Ser Ser Leu Glu Glu Cys Pro Ile Pro Lys Val Leu Ile Ser
 305 310 315 320
 Val Gly Ser Tyr Lys Ser Ser Val Glu Ser Val Leu Ile Lys Met Glu
 325 330 335
 Gln Glu Leu Gly Asp Glu Glu Tyr Lys Glu Val Glu Val Thr Glu Leu
 340 345 350
 Ser Ser Phe Asp Pro Gln Glu Asn Leu Asp Tyr Leu Asp Met Asp Met
 355 360 365
 Lys Gly Ser Ile Ser Ser Gly Glu Ser Ile Glu Val Leu Gly Thr Glu
 370 375 380
 Lys Ser Thr Ser Val Leu Ser Lys Ser Asp Ser Gln Ala Ser Leu Thr
 385 390 395 400
 Val Pro Leu Ser Pro Gln Val Val Arg Ser Lys Ala Val Ser His Arg
 405 410 415
 Thr Ile Ser Glu Asp Ser Ile Glu Val Leu Ser Thr
 420 425

<210> 122
 <211> 168
 <212> PRT
 <213> Homo sapiens

<400> 122
 Met Gly Glu Glu Ala Val Arg Trp Ala Lys Leu Val Ile Pro Leu Val
 1 5 10 15
 Val His Ser Ala Gln Lys Val His Leu Arg Gly Ala Thr Ala Leu Glu
 20 25 30
 Met Gly Met Pro Leu Leu Leu Gln Lys Gln Gln Glu Ile Ala Ser Ile
 35 40 45
 Thr Glu Gln Leu Met Thr Thr Thr Leu His Arg Ser Gly Ser Phe Ile
 50 55 60
 Asn Ser Leu Leu Gln Leu Glu Glu Leu Gly Phe Arg Ser Gly Ala Pro
 65 70 75 80
 Met Ile Lys Lys Ile Ala Phe Ile Ala Trp Lys Ser Leu Ile Asp Asn
 85 90 95
 Phe Ala Leu Asn Pro Asp Ile Leu Cys Ser Ala Lys Arg Leu Lys Leu
 100 105 110
 Leu Met Gln Pro Leu Ser Ser Ile His Val Arg Thr Glu Thr Leu Ala
 115 120 125
 Leu Thr Lys Leu Glu Val Trp Trp Tyr Leu Leu Met Arg Leu Gly Pro
 130 135 140
 His Leu Pro Ala Asn Phe Glu Gln Gly Cys Val Pro Leu Ile Gln Ser
 145 150
 ??
 ?? 55
 60
 Ser Leu Asp Phe Lys Phe Gly Arg Arg Ser Asn Arg Ala Asp Glu Leu
 65
 ??
 ?? 85
 90 95
 Ala Thr Ala Gly Asn Arg Gly Leu Ala Phe Pro Ser Arg His Ile AsnVal Ala Met
 Asp Thr Asp
 35 40 45
 Ser Glu Thr Ser Ser Pro Ala Pro Ser Pro Val Gln Pro Pro Phe Phe
 50 55 60
 Ser Glu Cys Ser Leu Gly Tyr Phe Ser Pro Ala Pro Ser Leu Ser Leu
 65 70 75 80
 Pro Pro Pro Pro Gln Val Ser Ser Leu Pro Pro Leu Ser Gln Pro Tyr
 85 90 95
 Val Glu Gly Leu Cys Val Ser Leu Glu Pro Leu Pro Pro Leu Pro Pro
 100 105 110
 Leu Pro Pro Leu Pro Pro Glu Asp Pro Glu Gln Pro Pro Lys Pro Pro
 115 120 125
 Phe Ala Asp Glu Glu Glu Glu Glu Glu Met Leu Leu Arg Glu Glu Leu
 130 135 140
 Leu Lys Ser Leu Ala Asn Lys Arg Ala Phe Lys Pro Glu Leu Pro Lys
 145 150 155 160
 His Lys Ser Val Val Thr Leu Asn Asp Ser Asp Asp Ser Glu Ser
 165 170 175
 Asp Gly Glu Ala Ser Lys Ser Thr Asn Ser Val Phe Gly Gly Leu Glu
 180 185 190
 Ser Met Ile Lys Glu Ala Arg Arg Thr Ala Glu Gln Ala Ser Lys Pro
 195 200 205
 Lys Val Pro Pro Lys Ser Glu Lys Glu Asn Asp Pro Leu Arg Thr Pro
 210 215 220
 Glu Ala Leu Pro Glu Glu Lys Lys Ile Glu Tyr Arg Leu Leu Lys Gly
 225 230 235 240

[illegible]

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<210> 124
<211> 123
<212> PRT
<213> Homo sapiens
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<400> 124															
Met	Cys	Pro	Phe	Cys	Ala	Asp	Arg	Asp	Ser	Val	Glu	Asp	Asp	Ile	Gln
1				5					10					15	
Phe	Phe	Asn	Gly	Val	Thr	Ala	Thr	Ser	Trp	Val	Gln	Gln	Gly	Val	Gly
			20					25					30		
Asp	Ser	Lys	Glu	Gln	Met	Ile	Gln	Ile	Arg	Val	Arg	Trp	Val	Gln	Arg
		35					40					45			
Asp	Thr	Leu	Gly	Ser	Arg	Pro	Thr	Arg	Leu	Pro	Val	Ser	Leu	Ser	Cys
	50					55					60				
Gly	Gly	Gly	Thr	Val	Ala	Phe	Val	Cys	Leu	Pro	Leu	Ala	Gln	Thr	Pro
65					70					75					80
Glu	Leu	Arg	Val	Gly	Lys	Met	Lys	Ala	Ala	Arg	Gly	Thr	Leu	Pro	Pro
				85					90					95	
Pro	Thr	Leu	Ser	Ser	Arg	Thr	Ser	Ala	Asn	Glu	Arg	Ala	Thr	Leu	Ala
			100					105					110		
Ser	Trp	Gly	Thr	Asp	His	Phe	Leu	Ser	Ser	Leu					
		115					120								

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<210> 125
<211> 104
<212> PRT
<213> Homo sapiens
```

<400> 125
 Met Val Trp Val Leu Leu Ala Trp Ser Thr Cys Pro Gly Leu Leu Gly
 1 5 10 15
 Phe Lys Pro Thr Val Glu Ile Glu Gly Thr Val Pro Trp Ser Pro Ala
 20 25 30

Gly Thr Ser Arg Val Leu Pro Thr Arg Val Ala Glu Ser Leu Gly Leu
 35 40 45
 Arg Val Thr Ser Gly Gly Thr Arg Ser Ser Ala Pro Glu Ala Pro Thr
 50 55 60
 Met Lys Gln Ser Asp Ala Ser Pro Gln Glu Arg Tyr Pro Pro Ala Ser
 65 70 75 80
 Pro Glu Thr Glu Trp Asp Pro Asn Gly Ile Phe Gly Gly Gly Glu Ser
 85 90 95
 Val Pro Gln Arg Glu Thr Ser Thr
 100

<210> 126
 <211> 147
 <212> PRT
 <213> Homo sapiens

<400> 126
 Met Gln Val Leu Ile Gln Gly Leu Glu Glu Pro Phe Gln Ala Gly Leu
 1 5 10 15
 Val Cys Val Leu Trp Asn Gly Val Gly Gln Ile Thr Ser Thr Ala Val
 20 25 30
 Phe Glu Gln Cys Val Trp Asn Ile Ala Leu His Gln Gly Cys His Thr
 35 40 45
 Ser His Val Val Gln Leu Met Gly Leu Gln Asn Arg Arg Leu Pro Arg
 50 55 60
 Glu Cys Gln Ala Glu Ser Leu Ala Ile Cys Leu Leu Gln Ala Gln Gly
 65 70 75 80
 Arg His Ala Ala Arg Glu Pro His Met Leu Glu His Gly His Ala Val
 85 90 95
 Thr Gln Arg Ile Arg Val Met Gln Met Ala Gly Cys Glu Tyr Asp Arg
 100 105 110
 Thr Thr Phe Ser Val Leu Gln Gln Asn Val Pro Gln Ala Met Thr Gly
 115 120 125
 Ala Arg Val His Pro Ala Gly Gly Leu Ile Gln Asn Gly Gly Pro Ala
 130 135 140
 His Gly His
 145

<210> 127
 <211> 532
 <212> PRT
 <213> Homo sapiens

<400> 127
 Met Ala Ser His Ala Tyr Asp Lys Asn Gln Asn Ala Asn Val Leu Val
 1 5 10 15
 His Leu Cys Phe Tyr Asn Arg Ile Pro Lys Thr Gly Ala Tyr Tyr Leu
 20 25 30
 Asp Ser Arg Ser Val Ser Ile Ser Tyr Leu Ile Gly His His Ile Asp
 35 40 45
 Met Gly Leu Glu Thr Ala Thr Ser Lys Asn Glu Phe Ile Phe Asp Ser
 50 55 60
 Ala Ser Thr Leu Leu Gly Met Leu Phe Arg Lys Pro Ser Gln His Ser
 65 70 75 80
 Leu Ser Leu Phe Ser Lys Lys Phe Gln Glu Asn Leu Ile Tyr Leu Glu
 85 90 95
 Ser Asp Asp Cys Leu Pro Pro Pro Pro Pro Pro Trp Ser Glu Pro
 100 105 110

Pro Ser Phe Leu Thr Trp Thr Ile Val Thr Val Phe Gln Trp Val Ser
 115 120 125
 Leu Leu Leu Ser Leu Pro Asn Ile Gln Val Ile Leu Tyr Arg Ala Val
 130 135 140
 Gly Val Val Pro Ser Gln Pro Lys Ser Asp Asn Leu Lys Gly Trp Gly
 145 150 155 160
 Ser Gly Arg Val Val Lys Glu Lys Leu Arg Ser Glu Ile Pro Asp Trp
 165 170 175
 Lys Ile Lys Ser Ile His Ile Leu Glu Arg Thr Ala Ser Ser Ser Thr
 180 185 190
 Glu Pro Ser Val Ser Arg Gln Leu Leu Glu Pro Glu Pro Val Pro Leu
 195 200 205
 Ser Lys Glu Ala Asp Ser Trp Glu Ile Ile Glu Gly Leu Lys Ile Gly
 210 215 220
 Gln Thr Asn Val Gln Lys Pro Asp Lys His Glu Gly Phe Met Leu Lys
 225 230 235 240
 Lys Arg Lys Trp Pro Leu Lys Gly Trp His Lys Ile Gln Lys Gly Lys
 245 250 255
 Val His Gly Ser Ile Asp Val Gly Leu Ser Val Met Ser Ile Lys Lys
 260 265 270
 Lys Ala Arg Arg Ile Asp Leu Asp Thr Glu Glu His Ile Tyr His Leu
 275 280 285
 Lys Val Lys Ser Val Phe Asn Ser Phe Ser Ala Ile Ile Arg Gly Asn
 290 295 300
 Asp Leu Pro Thr Pro Val Val Lys Ser Gln Asp Trp Phe Asp Ala Trp
 305 310 315 320
 Val Ser Lys Leu Arg His His Arg Leu Tyr Arg Gln Asn Glu Ile Val
 325 330 335
 Arg Ser Pro Arg Asp Ala Ser Phe His Ile Phe Pro Ser Thr Ser Thr
 340 345 350
 Ala Glu Ser Ser Pro Ala Ala Asn Val Ser Val Met Asp Gly Lys Met
 355 360 365
 Gln Pro Asn Ser Phe Pro Trp Gln Ser Pro Leu Pro Cys Ser Asn Ser
 370 375 380
 Leu Pro Ala Thr Cys Thr Thr Gly Gln Ser Lys Val Ala Ala Trp Leu
 385 390 395 400
 Gln Asp Ser Glu Glu Met Asp Arg Cys Ala Glu Asp Leu Ala His Cys
 405 410 415
 Gln Ser Asn Leu Val Glu Leu Ser Lys Leu Leu Gln Asn Leu Glu Ile
 420 425 430
 Leu Gln Arg Thr Gln Ser Ala Pro Asn Phe Thr Asp Met Gln Ala Asn
 435 440 445
 Cys Val Asp Ile Ser Lys Lys Asp Lys Arg Val Thr Arg Arg Trp Arg
 450 455 460
 Thr Lys Ser Val Ser Lys Asp Thr Lys Ile Gln Leu Gln Val Pro Phe
 465 470 475 480
 Ser Ala Thr Met Ser Pro Val Arg Leu His Ser Ser Asn Pro Asn Leu
 485 490 495
 Cys Ala Asp Ile Glu Phe Gln Thr Pro Pro Ser His Leu Thr Asp Pro
 500 505 510
 Leu Glu Ser Ser Thr Asp Tyr Thr Lys Leu Gln Glu Glu Phe Cys Leu
 515 520 525
 Ile Ala Gln Lys
 530

<210> 128
 <211> 210
 <212> PRT
 <213> Homo sapiens

<400> 128

```

Met Glu Gly Gly Phe Val Glu Val Ile His Asp Lys Lys Gln Tyr Pro
 1      5      10
Ile Ser Glu Leu Cys Lys Gln Phe Arg Leu Pro Phe Asn Val Lys Val
      20      25      30
Ser Val Arg Asp Leu Ser Ile Glu Asp Val Leu Ala Ala Thr Pro
      35      40      45
Gly Leu Gln Leu Glu Glu Asp Ile Thr Asp Ser Tyr Leu Leu Ile Ser
      50      55      60
Asp Phe Ala Asn Pro Thr Glu Cys Trp Glu Ile Pro Val Gly Arg Leu
      65      70      75      80
Asn Met Thr Val Gln Leu Val Ser Asn Phe Ser Arg Asp Ala Glu Pro
      85      90      95
Phe Leu Val Arg Thr Leu Val Glu Glu Ile Thr Glu Glu Gln Tyr Tyr
      100      105      110
Met Met Arg Arg Tyr Glu Ser Ser Ala Ser His Pro Pro Pro Arg Pro
      115      120      125
Pro Lys His Pro Ser Val Glu Glu Thr Lys Leu Thr Leu Leu Thr Leu
      130      135      140
Ala Glu Glu Arg Thr Val Asp Leu Pro Lys Ser Pro Lys Arg His His
      145      150      155      160
Val Asp Ile Thr Lys Lys Leu His Pro Asn Gln Ala Gly Leu Asp Leu
      165      170      175
Val Asp Glu Glu Lys Asp Arg Ser Asn Arg Gly Ala Thr Ala Leu Ala
      180      185      190
Glu Thr Phe Asn Asn Asp Lys His His Lys Tyr Gln Asp Val Thr Glu
      195      200      205
Ala Thr
      210

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<210> 129
<211> 515
<212> PRT
<213> Homo sapiens

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```

<400> 129
Met Phe Ala Phe Glu Pro Leu Gly Gly Cys Arg Pro Trp Arg Leu Ser
 1      5      10
Leu Pro Gly Pro Gly Ser Arg Leu Phe Arg Thr Tyr Gly Ala Ala Asp
      20      25      30
Gly Arg Arg Gln Arg Arg Pro Gly Arg Glu Ala Ala Gln Trp Phe Pro
      35      40      45
Pro Gln Asp Arg Arg Arg Phe Phe Asn Ser Ser Gly Ser Ser Asp Ala
      50      55      60
Ser Ile Gly Asp Pro Ser Gln Ser Asp Asp Pro Asp Asp Pro Asp Asp
      65      70      75      80
Pro Asp Phe Pro Gly Ser Pro Val Arg Arg Arg Arg Cys Pro Gly
      85      90      95
Gly Arg Val Pro Lys Asp Arg Pro Ser Leu Thr Val Thr Pro Lys Arg
      100      105      110
Trp Lys Leu Arg Ala Arg Pro Ser Leu Thr Val Thr Pro Arg Arg Leu
      115      120      125
Gly Leu Arg Ala Arg Pro Pro Gln Lys Cys Ser Thr Pro Cys Gly Pro
      130      135      140
Leu Arg Leu Pro Pro Phe Pro Ser Arg Asp Ser Gly Arg Leu Ser Pro
      145      150      155      160
Asp Leu Ser Val Cys Gly Gln Pro Arg Asp Gly Asp Glu Leu Gly Ile
      165      170      175
Ser Ala Ser Leu Phe Ser Ser Leu Ala Ser Pro Cys Pro Gly Ser Pro
      180      185      190
Thr Pro Arg Asp Ser Val Ile Ser Ile Gly Thr Ser Ala Cys Leu Val
      195      200      205

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Ala Ala Ser Ala Val Pro Ser Gly Leu His Leu Pro Glu Val Ser Leu
 210 215 220
 Asp Arg Ala Ser Leu Pro Cys Ser Gln Glu Glu Ala Thr Gly Gly Ala
 225 230 235 240
 Lys Asp Thr Arg Met Val His Gln Thr Arg Ala Ser Leu Arg Ser Val
 245 250 255
 Leu Phe Gly Leu Met Asn Ser Gly Thr Pro Glu Asp Ser Glu Phe Arg
 260 265 270
 Ala Asp Gly Lys Asn Met Arg Glu Ser Cys Cys Lys Arg Lys Leu Val
 275 280 285
 Val Gly Asn Gly Pro Glu Gly Pro Gly Leu Ser Ser Thr Gly Lys Arg
 290 295 300
 Arg Ala Thr Gly Gln Asp Ser Cys Gln Glu Arg Gly Leu Gln Glu Ala
 305 310 315 320
 Val Arg Arg Glu His Gln Glu Ala Ser Val Pro Lys Gly Arg Ile Val
 325 330 335
 Pro Arg Gly Ile Asp Arg Leu Glu Arg Thr Arg Ser Ser Arg Lys Ser
 340 345 350
 Lys His Gln Glu Ala Thr Glu Thr Ser Leu Leu His Ser His Arg Phe
 355 360 365
 Lys Lys Gly Gln Lys Leu Gly Lys Asp Ser Phe Pro Thr Gln Asp Leu
 370 375 380
 Thr Pro Leu Gln Asn Ala Cys Phe Trp Thr Lys Thr Arg Ala Ser Phe
 385 390 395 400
 Ser Phe His Lys Lys Lys Ile Val Thr Asp Val Ser Glu Val Cys Ser
 405 410 415
 Ile Tyr Thr Thr Ala Thr Ser Leu Ser Gly Ser Leu Leu Ser Glu Cys
 420 425 430
 Ser Asn Arg Pro Val Met Asn Arg Thr Ser Gly Ala Pro Ser Ser Trp
 435 440 445
 His Ser Ser Ser Met Tyr Leu Leu Ser Pro Leu Asn Thr Leu Ser Ile
 450 455 460
 Ser Asn Lys Lys Ala Ser Asp Ala Glu Lys Val Tyr Gly Glu Cys Ser
 465 470 475 480
 Gln Lys Gly Pro Val Pro Phe Ser His Cys Leu Pro Thr Glu Lys Leu
 485 490 495
 Gln Arg Cys Glu Lys Ile Gly Glu Gly Val Phe Gly Gly Ser Val Ser
 500 505 510
 Asn Asn Cys
 515

<210> 130
 <211> 155
 <212> PRT
 <213> Homo sapiens

<400> 130
 Met Asn Gly Arg Lys Glu Glu Gly Glu Arg Leu Thr Lys Glu Val Met
 1 5 10 15
 Ser Ser Tyr Ile Gln Ser Glu Phe Ala Ser Val Cys Thr Ser Asn Ser
 20 25 30
 Ile Leu Asp Leu Phe Arg Thr Pro Ala Ile Arg Lys Val Thr Cys Cys
 35 40 45
 Leu Met Val Ile Trp Arg Met Ala Pro Pro Ala Gly Arg Glu Leu Arg
 50 55 60
 Ile Ala Ala Glu Ser Leu Ser Gln Gln Lys Arg Ala Phe Ala Val Ser
 65 70 75 80
 Arg Arg Ile Gln Glu Arg Thr Phe Ser Ser Gly Ile Leu Asn Ser Gly
 85 90 95
 Ser Val Ser Pro Ser Arg Lys Glu Glu Gly Gly Arg Arg Ala Ser Pro
 100 105 110

Gly Arg Gln Gly Leu Pro Gln Glu Asp Ala His Ser Trp Thr Arg Val
 115 120 125
 Arg Arg Ser Pro Leu Ala Pro Gln Ser Arg Asn Cys Ala Ala Cys His
 130 135 140
 Ala Arg Leu Thr Pro Arg Lys Ser Arg Ala Thr
 145 150 155

<210> 131
 <211> 145
 <212> PRT
 <213> Homo sapiens

<400> 131
 Met Leu Asp Gln Cys Arg Thr Leu Ala Ser Arg Gly Thr Pro Pro Cys
 1 5 10 15
 Lys Pro Ser Cys Val Ser Gln Leu Gly Gln Arg Ala Glu Pro Lys Ala
 20 25 30
 Thr Glu Arg Gly Ile Leu Arg Ala Thr Cys Val Ala Trp Glu Ser Gln
 35 40 45
 Leu Lys Pro Glu Glu Leu Pro Ser Met Gln Asp Leu Leu Glu Glu Ala
 50 55 60
 Ser Ser Arg Asp Met Gln Met Gly Pro Gly Leu Phe Leu Arg Met Gln
 65 70 75 80
 Leu Val Pro Ser Ile Glu Glu Arg Glu Thr Pro Leu Thr Arg Glu Asp
 85 90 95
 Arg Pro Ala Leu Gln Glu Pro Pro Trp Ser Leu Gly Cys Thr Gly Leu
 100 105 110
 Lys Ala Ala Met Gln Ile Gln Arg Val Val Ile Pro Val Pro Thr Leu
 115 120 125
 Gly His Arg Asn Pro Trp Val Ala Arg Asp Ser Gly Ala Ile Gly Asn
 130 135 140
 Gly
 145

<210> 132
 <211> 288
 <212> PRT
 <213> Homo sapiens

<400> 132
 Met Asp Ala Ala Val Thr Asp Asp Phe Gln Gln Ile Leu Pro Ile Glu
 1 5 10 15
 Gln Leu Arg Ser Thr His Ala Ser Asn Asp Tyr Val Glu Arg Pro Pro
 20 25 30
 Ala Pro Cys Lys Gln Ala Leu Ser Ser Pro Ser Leu Ile Val Gln Thr
 35 40 45
 His Lys Ser Asp Trp Ser Leu Ala Thr Met Pro Thr Ser Leu Pro Arg
 50 55 60
 Ser Leu Ser Gln Cys His Gln Leu Gln Pro Leu Pro Gln His Leu Ser
 65 70 75 80
 Gln Ser Ser Ile Ala Ser Ser Met Ser His Ser Thr Thr Ala Ser Asp
 85 90 95
 Gln Arg Leu Leu Ala Ser Ile Thr Pro Ser Pro Ser Gly Gln Ser Ile
 100 105 110
 Ile Arg Thr Gln Pro Gly Ala Gly Val His Pro Lys Ala Asp Gly Ala
 115 120 125
 Leu Lys Gly Glu Ala Glu Gln Ser Ala Gly His Pro Ser Glu His Leu
 130 135 140


```

Phe Ile Cys Glu Glu Cys Gly Arg Cys Lys Cys Val Pro Cys Thr Ala
145          150          155          160
Ala Arg Pro Leu Pro Ser Cys Trp Leu Cys Asn Gln Arg Cys Leu Cys
          165          170          175
Ser Ala Glu Ser Leu Leu Asp Tyr Gly Thr Cys Leu Cys Cys Val Lys
          180          185          190
Gly Leu Phe Tyr His Cys Ser Thr Asp Asp Glu Asp Asn Cys Ala Asp
          195          200          205
Glu Pro Cys Ser Cys Gly Pro Ser Ser Cys Phe Val Arg Trp Ala Ala
          210          215          220
Met Ser Leu Ile Ser Leu Phe Leu Pro Cys Leu Cys Cys Tyr Leu Pro
225          230          235          240
Thr Arg Gly Cys Leu His Leu Cys Gln Gln Gly Tyr Asp Ser Leu Arg
          245          250          255
Arg Pro Gly Cys Arg Cys Lys Arg His Thr Asn Thr Val Cys Arg Lys
          260          265          270
Ile Ser Ser Gly Ser Ala Pro Phe Pro Lys Ala Gln Glu Lys Ser Val
          275          280          285

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<210> 133
<211> 255
<212> PRT
<213> Homo sapiens

```

```

<400> 133
Met Glu Asn Glu Lys Glu Asn Leu Phe Cys Glu Pro His Lys Arg Gly
1          5          10          15
Leu Met Lys Thr Pro Leu Lys Glu Ser Thr Thr Ala Asn Ile Val Leu
          20          25          30
Ala Glu Ile Gln Pro Asp Phe Gly Pro Leu Thr Thr Pro Thr Lys Pro
          35          40          45
Lys Glu Gly Ser Gln Gly Glu Pro Trp Thr Pro Thr Ala Asn Leu Lys
50          55          60
Met Leu Ile Ser Ala Val Ser Pro Glu Ile Arg Asn Arg Asp Gln Lys
65          70          75          80
Arg Gly Leu Phe Asp Asn Arg Ser Gly Leu Pro Glu Ala Lys Asp Cys
          85          90          95
Ile His Glu His Leu Ser Gly Asp Glu Phe Glu Lys Ser Gln Pro Ser
          100          105          110
Arg Lys Glu Lys Ser Leu Gly Leu Leu Cys His Lys Phe Leu Ala Arg
          115          120          125
Tyr Pro Asn Tyr Pro Asn Pro Ala Val Asn Asn Asp Ile Cys Leu Asp
130          135          140
Glu Val Ala Glu Glu Leu Asn Val Glu Arg Arg Ile Tyr Asp Ile
145          150          155          160
Val Asn Val Leu Glu Ser Leu His Met Val Ser Arg Leu Ala Lys Asn
          165          170          175
Arg Tyr Thr Trp His Gly Arg His Asn Leu Asn Lys Thr Leu Gly Thr
          180          185          190
Leu Lys Ser Ile Gly Glu Glu Asn Lys Tyr Ala Glu Gln Ile Met Met
          195          200          205
Ile Lys Lys Lys Glu Tyr Glu Gln Glu Phe Asp Phe Ile Lys Ser Tyr
210          215          220
Ser Ile Glu Asp His Ile Ile Lys Ser Asn Thr Gly Pro Asn Gly His
225          230          235          240
Pro Asp Met Cys Phe Val Glu Leu Pro Gly Val Glu Phe Arg Ala
          245          250          255

```

<210> 134
 <211> 68
 <212> PRT
 <213> Homo sapiens

<400> 134
 Met Gly Thr Arg Pro Leu His Gly His Lys Leu Ser Arg Trp Asn Ile
 1 5 10 15
 Met Ser Ser Asn Phe Ser Ser Thr Gly Leu Lys Asp Phe Asn Thr Pro
 20 25 30
 Lys Ala Leu Phe Ile Arg Lys Gly Leu Gly Arg Gly Glu Lys Thr Leu
 35 40 45
 Val His Phe Ile Gln Val Phe Ser Tyr Thr Arg Lys Gln Ser Ser His
 50 55 60
 Ser His Glu Asn
 65

<210> 135
 <211> 211
 <212> PRT
 <213> Homo sapiens

<400> 135
 Met Tyr Asp Ile Phe Asn Leu Asn Asp Lys Ala Leu Cys Phe Thr Lys
 1 5 10 15
 Cys Arg Gln Ser Gly Ser Asp Ser Cys Asn Val Glu Asn Leu Gln Arg
 20 25 30
 Tyr Trp Leu Asn Tyr Glu Ala His Leu Met Lys Glu Gly Leu Thr Gln
 35 40 45
 Lys Val Asn Thr Pro Phe Leu Lys Ala Leu Val Gln Asn Leu Ser Thr
 50 55 60
 Asn Thr Ala Glu Asp Phe Tyr Leu Ser Leu Glu Pro Ser Gln Val Pro
 65 70 75 80
 Arg His Val Met Lys Asp Glu Asp Lys Pro Pro Asp Arg Val Arg Leu
 85 90 95
 Pro Lys Ser Leu Phe Arg Ser Leu Pro Gly Asn Arg Ser Val Val Arg
 100 105 110
 Leu Ala Val Thr Ile Leu Asp Ile Gly Pro Gly Thr Leu Phe Lys Gly
 115 120 125
 Pro Arg Leu Gly Leu Gly Asp Gly Ser Gly Val Leu Asn Asn Arg Leu
 130 135 140
 Val Gly Leu Ser Val Gly Gln Met His Val Thr Lys Leu Ala Glu Pro
 145 150 155 160
 Leu Glu Ile Val Phe Ser His Gln Arg Pro Pro Lys Pro Thr Met
 165 170 175
 His Ser Glu Ile Thr Ser Ser Ile Phe Asn Arg Ile Ser Met Thr Cys
 180 185 190
 Thr Thr Tyr Tyr Tyr Ser Ser Thr Arg Tyr Lys Tyr Asn Asn Ile Ile
 195 200 205
 His Lys Asp
 210

<210> 136
 <211> 147
 <212> PRT
 <213> Homo sapiens

<400> 136
 Met Ser Cys Met Cys Trp Pro Asn Met Leu Asn His Gly Glu Leu Glu
 1 5 10 15
 Gln Ala Leu Leu Leu Lys Leu Leu Ile Met Leu Cys Thr Asn Leu
 20 25 30
 Glu Ser Ile Gln Ala Gly Arg Arg Gln Val Leu Glu His Arg Val Leu
 35 40 45
 Ser Leu Trp Thr Arg Tyr Leu Ala Glu Leu Lys Gly Cys Pro Pro Pro
 50 55 60
 Gln Gly Arg Gly Thr Gln Leu Glu Asn Val Ala Leu His Ala Leu Leu
 65 70 75 80
 Leu Cys Glu Gly Leu Phe Asp Pro Tyr Gln Thr Trp Arg Arg Gln Arg
 85 90 95
 Ser Gly Glu Val Ile Ser Ser Lys Glu Lys Ser Lys Tyr Lys Phe Pro
 100 105 110
 Pro Ala Ala Leu Pro Gln Glu Phe Ser Ala Phe Phe Gln Gly Gln Ala
 115 120 125
 Pro Pro Leu Pro Pro Leu Gly Ser Thr Pro Lys Pro Arg Pro Leu Pro
 130 135 140
 Val Val Pro
 145

<210> 137
 <211> 36
 <212> PRT
 <213> Homo sapiens

<400> 137
 Met Ser Gly Arg Val Phe Arg Cys Gln Ala Leu Val Ala Tyr Thr Val
 1 5 10 15
 Leu Ser Glu Leu Phe Thr Glu Ala Lys Glu Gln Arg Leu Ala Thr Asp
 20 25 30
 Glu Gly Gln Lys
 35

<210> 138
 <211> 41
 <212> PRT
 <213> Homo sapiens

<400> 138
 Met Ser Gly Arg Val Phe Arg Cys Gln Ala Leu Val Ala Tyr Thr Val
 1 5 10 15
 Leu Ser Glu Leu Phe Thr Glu Ala Lys Glu Gln Arg Leu Ala Thr Asp
 20 25 30
 Glu Gly Gln Lys Glu Phe Ser Ala Glu
 35 40

<210> 139
 <211> 100
 <212> PRT
 <213> Homo sapiens

<400> 139

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Met Gln Lys Arg Leu Lys Val Val Thr Thr Val Leu Thr Asp Ala Ser
 1          5          10          15
Lys Gly Ser Leu Asp Gln Gly Ser Glu Ala Thr Ser Ala Asn Ser Leu
          20          25          30
Cys Gly Ala Cys Val Cys Ala Ser Ser Glu Leu Arg Ser His Gly Leu
          35          40          45
Ser Arg Ser Asp Gly Ser Ser Asp Ser Phe His Val Pro Trp Leu His
          50          55          60
Gly Ala His Ala Leu Val Leu Leu Pro Asn Ala Gly Ala Ala Glu Ser
          65          70          75          80
Pro Leu Ala Arg Pro His Pro Arg Glu Thr His Val Gly Ala Val Pro
          85          90          95
Glu Asp Ser Leu
          100

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<210> 140
<211> 53
<212> PRT
<213> Homo sapiens

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```

<400> 140
Met Ser Leu Lys Gln Ala Leu Gln Ser Pro Gly Leu Phe Leu Pro Ala
 1          5          10          15
Leu Ala Pro Ala Pro Ser Ser Ser Cys Val Gln Asn Gln Ser Gln Arg
          20          25          30
Cys Gly Leu Asn Pro Gly Ser Cys Pro Asp Thr Trp Leu Thr Ser Ser
          35          40          45
Phe Ser Leu Pro Ser
          50

```

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<210> 141
<211> 419
<212> PRT
<213> Homo sapiens

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<400> 141
Met Glu Ala Ala Asp Val Ala His Arg Ala His Met Ser Gln Lys Ala
 1          5          10          15
Gly Gly Phe Arg Asn Ile Ala Ile Gln Thr Ser Pro Ser Leu Arg Lys
          20          25          30
His Phe Pro Val Phe Lys Arg Lys Arg Leu Thr Ala Ser Lys Ser Leu
          35          40          45
Val Glu Met Pro Thr Ala Ser Gln Ser Ala Ile Gln Val Asn Gly Asn
          50          55          60
Leu Ser Glu Gln Asp Ile Val Ser Ser Asp Leu Ala Tyr Leu Arg Leu
          65          70          75          80
Ala Gln His Leu Glu Asp Gly Pro Arg Arg Val Lys Val Ser His Ala
          85          90          95
Phe Leu Pro Arg Val Pro Lys Val Gln Ser Asn Gly Pro Val Ser Ile
          100          105          110
Cys Leu Glu Ala Gly Thr Trp Arg Ser Leu Glu Lys Ala Thr Ala Ala
          115          120          125
Ile Gln Val Pro Asp Asp Ile Tyr His Ser Pro Ser Trp Glu Ala Arg
          130          135          140
Glu Ser Ala Leu Ser Pro Asp Arg Ser Ala Glu Val Ser Asn Ser Ile
          145          150          155          160
His Pro Leu Asp Asp Thr Arg Pro Gly Asp Gly Arg Arg Val Thr Pro
          165          170          175

```

Leu Asp Ser Glu Lys Ser Thr Ser Cys Leu Asn Ala Thr Ser Val Ala
 180 185 190
 Ser His Thr Pro Gly Thr Glu Glu Leu Lys Pro Glu Leu Leu Leu Pro
 195 200 205
 Lys Asp Asn Ser Asp Asp Lys Asp Leu Gly Ser Leu Ser Ser Gln Ser
 210 215 220
 Lys Glu Thr Cys Val Pro Ser Ser Pro Arg Thr His Ser Ser Pro Ser
 225 230 235 240
 Gln Gly Ser His Ser Gln Pro Ala His Pro Gly Arg Ala Ser Asp Cys
 245 250 255
 Pro Ser Ser Ser Asn Asn His Gln Asn Leu Val Ser Leu Lys Thr Asn
 260 265 270
 Ser Ala Ser Lys Ser Ala Pro Gly Cys Gln Glu Gln Thr Ala Asn Asn
 275 280 285
 Pro Thr Glu Ser Asp Thr Leu Glu Phe Pro Asn Cys Pro Gly Ser Asn
 290 295 300
 His Leu Pro Ser Ser Leu Ser Arg Ser Glu Thr Lys Leu Gln Ser Asn
 305 310 315 320
 Arg Glu Ile Ser Asp Ile Asn Gln Ile His Leu Ala Arg Gly Glu Leu
 325 330 335
 Cys Asp Leu Gln Gly Arg Leu Gln Ser Val Glu Glu Ser Leu His Ser
 340 345 350
 Asn Gln Glu Lys Ile Lys Val Leu Leu Asn Val Ile Gln Asp Leu Glu
 355 360 365
 Lys Ala Arg Ala Leu Thr Glu Gly Leu Leu Gly Ser Pro Leu Thr Ile
 370 375 380
 Glu His Leu Asp Thr Ser Tyr Leu Thr Lys Ser Thr Asp Pro Thr Pro
 385 390 395 400
 Met Pro Arg Asp Ser Ile His Gly Ser Gln Glu Leu Ala Gly Ile Ser
 405 410 415
 Val His Lys

<210> 142
 <211> 270
 <212> PRT
 <213> Homo sapiens

<400> 142
 Met Asp Ser Gln Glu Val Glu Lys Tyr Pro Asn Thr Ser Val Ala Cys
 1 5 10 15
 Glu Glu Ile Pro Phe Ser Gly Ile His Val Ala Gly Gly Lys Ser Gly
 20 25 30
 Ala Leu Glu His Gly Lys Asp Asp Leu Asp Glu Pro Ile Glu Asn Pro
 35 40 45
 Leu Phe Cys Phe Ser Ser Phe Ser Asn Ala Leu Ala Ile Leu Leu Pro
 50 55 60
 Lys Val Phe Leu Lys Asn Ile His Ile Leu Gln Phe Ile Tyr Arg Ser
 65 70 75 80
 Phe His Leu Leu Thr Met Ala Lys Ala Lys Phe Glu Gly Ala Glu Ser
 85 90 95
 Val Glu Pro Val Ser Pro Ser Gln Pro Lys Arg Pro Ser Tyr Val Pro
 100 105 110
 Leu Glu Glu Leu Trp Thr Arg Leu Thr Lys Gly Asn Ser Arg Pro Gln
 115 120 125
 Gln Arg Asp Arg Glu Lys Gly Gly Trp Met Lys Gly Val Gln Gln Gly
 130 135 140
 His Gln Gly Val Gly Lys Gln Glu Glu Gly Ser Glu Asn Ile Lys Glu
 145 150 155 160
 Lys Ala Gly Asn Trp Gly Asp Gly Arg Arg Trp Gly Arg Asn Gln Gln
 165 170 175

```

Val Leu Ile Asn Lys Ile Thr Phe Lys Gln Thr Ser Leu Asn Tyr Thr
      180      185      190
Ser Asn Leu Val Phe Pro Glu Glu Ser Tyr Phe Ser Asn Ala Tyr Ser
      195      200      205
Leu Ser Trp Thr His Ile Val Leu His His Cys Glu Ile His Leu Arg
      210      215      220
Lys Val Lys Ile Gly Cys Leu Leu Arg Glu Thr Asn Leu Lys Val Arg
      225      230      235      240
His Ala Leu Ser Val Thr Ser Glu Leu Gly Ala Asp Ile Ser Arg Leu
      245      250      255
Ala Gly Phe Asp Glu Ala Tyr Lys Leu Thr Ser Ile Gly Ser
      260      265      270

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<210> 143
<211> 78
<212> PRT
<213> Homo sapiens

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      <400> 143
Met Gly Leu Cys Ile Thr Ser Ile Ala Thr Trp Ser Ala Ala Gly Ser
  1      5      10      15
Pro Thr Gly Cys Leu Ser Ile Lys Tyr Phe Ser Thr Gly Arg Ser Ser
      20      25      30
Ser Phe Arg Ala Leu Lys Glu Leu Cys Cys Leu Phe Pro Gly Leu Cys
      35      40      45
Leu Pro Thr Ser Leu Thr Val Ile Leu Ala Gly Asn Ile Leu Leu Gln
      50      55      60
Lys Thr Leu Trp Leu Phe Val Leu Ile Ser Phe Pro Pro Leu
      65      70      75

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<210> 144
<211> 80
<212> PRT
<213> Homo sapiens

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      <400> 144
Met Thr Ile Val Arg Asn Gly Val Arg Asp Lys Asp Ile Thr Ala Asp
  1      5      10      15
Ile Lys Arg Ile Ile Arg Glu Tyr Tyr Glu Gln Phe His Ile His Lys
      20      25      30
Phe Thr Lys Ile Gly Asn Ala Tyr Ala Val Leu Ser Asn Pro Glu Lys
      35      40      45
Arg Lys Gln Tyr Asp Leu Thr Gly Asn Glu Glu Gln Ala Cys Asn His
      50      55      60
Gln Asn Asn Gly Arg Phe Asn Phe His Arg Gly Phe Val Lys Leu Ile
      65      70      75      80

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<210> 145
<211> 219
<212> PRT
<213> Homo sapiens

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```

<400> 145

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Met  Pro  Lys  Lys  Asp  Asp  Ser  Asn  Trp  Gly  Tyr  Ala  Phe  Thr  Asp  Gly
 1          5          10          15
Glu  Gln  Leu  Gly  Gly  Pro  Ser  Ala  Lys  Gly  Lys  Ile  Lys  Trp  Gln  Pro
          20          25          30
Thr  Ile  Cys  Thr  Trp  Pro  Thr  Phe  Ala  Lys  Glu  Ser  Gly  Arg  Ser  Leu
          35          40          45
Ser  Leu  Pro  Gly  Arg  Ser  Val  Pro  Pro  Pro  Ile  Ser  Thr  Ser  Pro  Trp
          50          55          60
Val  Tyr  Gln  Pro  Thr  Tyr  Ser  Tyr  Ser  Ser  Lys  Pro  Thr  Asp  Gly  Leu
          65          70          75          80
Glu  Lys  Ala  Asn  Lys  Arg  Pro  Thr  Pro  Trp  Glu  Ala  Ala  Ala  Lys  Ser
          85          90          95
Pro  Leu  Gly  Leu  Val  Asp  Asp  Ala  Phe  Gln  Pro  Arg  Asn  Ile  Gln  Glu
          100          105          110
Ser  Ile  Val  Ala  Asn  Val  Val  Ser  Ala  Ala  Arg  Arg  Lys  Val  Leu  Pro
          115          120          125
Gly  Pro  Pro  Glu  Asp  Trp  Asn  Glu  Arg  Leu  Ser  Tyr  Ile  Pro  Gln  Thr
          130          135          140
Gln  Lys  Ala  Tyr  Met  Gly  Ser  Cys  Gly  Arg  Gln  Glu  Tyr  Asn  Val  Thr
          145          150          155          160
Ala  Asn  Asn  Asn  Met  Ser  Thr  Thr  Ser  Gln  Tyr  Gly  Ser  Gln  Leu  Pro
          165          170          175
Tyr  Ala  Tyr  Tyr  Arg  Gln  Ala  Ser  Arg  Asn  Asp  Ser  Ala  Ile  Met  Ser
          180          185          190
Met  Glu  Thr  Arg  Ser  Asp  Tyr  Cys  Leu  Pro  Val  Ala  Asp  Tyr  Asn  Tyr
          195          200          205
Asn  Pro  His  Pro  Arg  Gly  Trp  Arg  Arg  Gln  Thr
          210          215

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<210> 146
<211> 214
<212> PRT
<213> Homo sapiens

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```

<400> 146
Met  Gly  Ala  Lys  Ala  Asp  Ser  Leu  Ala  Cys  Phe  Ser  Asp  Glu  Arg  Ser
 1          5          10          15
Arg  Gly  Ser  Gln  Arg  Gln  Phe  Ala  Lys  Glu  Asp  Gln  Ser  Leu  Arg  Arg
          20          25          30
Ser  Phe  Gly  Gly  Lys  His  Ala  Val  Ser  Ala  Val  Gly  Gly  Ser  Ala  Tyr
          35          40          45
Gln  His  His  Pro  Arg  Gly  Arg  Leu  Leu  Asp  Ala  Asp  Lys  Phe  His  Pro
          50          55          60
Leu  Ala  Asn  Pro  Lys  Ala  Thr  His  Val  Tyr  Met  Gly  Arg  Ala  Val  Arg
          65          70          75          80
His  Arg  Cys  Thr  Ala  Asp  Leu  Ser  Ala  Leu  Pro  Leu  Met  Phe  Leu  Leu
          85          90          95
Phe  Pro  Cys  Thr  Lys  Glu  Leu  Ser  Lys  Gln  Gln  Val  Arg  Arg  Gln  Gly
          100          105          110
His  Gly  Gly  Ser  Arg  Pro  Ala  Asp  Lys  Asp  Leu  Glu  Glu  Gly  Gly  Gly
          115          120          125
Leu  Glu  Ala  Glu  Ser  Pro  Lys  Gln  Ser  Pro  Asn  Leu  Cys  Val  Ile  Leu
          130          135          140
Arg  His  Asn  Leu  Ala  Ser  Arg  Pro  Gly  Gln  Leu  Ala  Leu  Val  Thr  Val
          145          150          155          160
Gly  Thr  Met  Gln  Gly  Arg  Pro  Leu  Ser  His  Ser  Ser  Glu  Val  Lys  Gly
          165          170          175
Thr  Thr  Phe  Val  Thr  His  Ser  Val  Pro  Ala  Gly  Lys  Glu  Lys  Asp  Glu
          180          185          190
Glu  Arg  Gly  Ile  Gly  Asp  Leu  Glu  His  Ala  Arg  Asp  Leu  Arg  Asn  Ser
          195          200          205

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Pro Thr Pro Leu Phe Tyr
210

<210> 147
<211> 125
<212> PRT
<213> Homo sapiens

<400> 147
Met Arg Val Pro Trp Ser Lys Cys Leu Ser Ala Gly Met Pro Leu Pro
1 5 10 15
Ser Gln Arg Leu Trp Leu Ser Glu Leu Ile Tyr Leu Lys Phe Leu Ala
20 25 30
Ser Gly Leu Phe Asn Gly Tyr Pro Asn Pro Glu Asn Phe Ser Trp Thr
35 40 45
Glu Tyr Leu Glu Ala Thr Gln Thr Asn Ala Val Pro Ala Lys Val Phe
50 55 60
Lys Met Asp Ser Asp Val Gly Glu Asn Arg Lys Ile Leu Arg Asp Glu
65 70 75 80
Arg Pro Asn Tyr Ser Gln Tyr Thr Pro Phe Ser Arg Cys Asp Asn Ala
85 90 95
Ser Tyr Lys Glu Asn Val Phe Leu Gln Lys Leu Glu Arg Asn Thr Pro
100 105 110
Asp Ile Ala Glu Arg Phe Asp Cys Leu Leu Leu Thr Tyr
115 120 125

<210> 148
<211> 126
<212> PRT
<213> Homo sapiens

<400> 148
Met Cys Lys Ser Trp Gln Cys Ser Val Asn Ala Gln Leu Gln Pro His
1 5 10 15
Leu Gly Leu Leu Gly Ser Leu Trp Val Met Leu Pro Ser Leu Val Gln
20 25 30
Leu Ala Ile Ala Arg Arg Lys Val Trp Pro Phe Gly Pro Glu Pro Gly
35 40 45
His Leu Ile Ser Glu Phe Gly His Phe Glu Gly Thr Val Leu Asp Lys
50 55 60
Pro Ser Trp Val Thr Cys Arg Ile Leu Gly Gly Gly Arg Leu Gln Gly
65 70 75 80
Met Gly Trp Leu Thr Ile Asp Phe Ser Pro Gln Ala Ser Lys Arg Ala
85 90 95
Leu Thr Ser Ser Ile Met Glu Leu Gly Pro Gly Val Ser Lys Leu Val
100 105 110
Gln Trp Gln Leu Glu Asn Leu Lys Arg His Cys Gly Pro Leu
115 120 125

<210> 149
<211> 53
<212> PRT
<213> Homo sapiens

<400> 149


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Met Arg Lys Pro Arg Leu Val Lys Ile Leu Gln Val Ala Gln Gly Pro
 1           5           10           15
His Arg Leu Arg Asp Lys Ala Arg Leu Gln Ile Gln Ala Ser Val Thr
           20           25           30
Leu Glu Cys Val Asp Ser Pro Leu Gln Tyr Thr Thr Ser His His Pro
           35           40           45
Cys Lys Lys Lys Lys
      50

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<210> 150
<211> 86
<212> PRT
<213> Homo sapiens

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<400> 150
Met Phe Leu Glu Arg Ile Gly Ile Val Leu Cys Glu Arg Glu Phe His
 1           5           10           15
Phe Glu Phe Leu Pro Gly Val Val Phe Gly Phe Val Lys Cys Phe Thr
           20           25           30
Val Met Val Val Leu Arg Lys Cys Ile Gln Ser Leu Leu Tyr Phe Leu
           35           40           45
Cys Thr Ala Asn Phe Met Gly Leu Pro Ser Arg Ala Gly Thr Glu Leu
           50           55           60
Ala Ala Tyr Thr Asn Arg Asn Ser Ser Thr Pro Pro Asp Thr Ala Glu
           65           70           75           80
Ala Ser Pro Cys Tyr Arg
              85

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<210> 151
<211> 149
<212> PRT
<213> Homo sapiens

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<400> 151
Met Glu Ser Pro Cys Asn Thr Gly Cys Ser Tyr Gly Asn Cys Tyr Lys
 1           5           10           15
Thr Arg Ser Gly Phe Thr Arg Val Gly Arg Arg Asn Leu Pro Arg Lys
           20           25           30
Pro Gly Ala Gly Val Met Gly Val Asp Val Leu Leu Gly Pro Arg Lys
           35           40           45
Val Gly Ser Asp Glu Glu Ala Leu Lys Lys Ser Gln Tyr Asp Asp Asp
           50           55           60
Ala Phe Met Val Lys Phe Cys Ala Ser Ser Thr Glu His Phe Leu Asn
           65           70           75           80
Asn Pro Gln Thr Asp Ala Val Leu Gly Gln Arg Tyr Gly Arg Glu Ser
           85           90           95
Lys Ser Pro Lys Cys Leu Asn His Lys His Arg Asp Leu Thr Pro Val
           100          105          110
Thr Val Glu Thr Asn Ala Leu Ala Ser Asp Pro Tyr Arg Ser Ala Phe
           115          120          125
Leu Pro Leu Asn Gly Ala Val Arg Gly Glu Leu Gly Cys Arg Thr Gly
           130          135          140
Gly Glu Lys Asn Val
      145

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<210> 152

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<211> 48
 <212> PRT
 <213> Homo sapiens

<400> 152
 Met Met Gly Met Tyr Leu Lys Pro Ser Glu Ser His Pro Asp Ser Gly
 1 5 10 15
 Glu Glu Pro Leu Lys Asp Glu Lys Asp Lys Gly Val Thr Arg Gly Gly
 20 25 30
 Gly Val Val His Cys Asp Ser Ser Ala Val Ala Leu Cys Val His Phe
 35 40 45

<210> 153
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 153
 Met His Glu Ser Asn Ala Ile Arg Ile Thr Val Glu Leu Phe Tyr Leu
 1 5 10 15
 Tyr Ala Ser Cys Arg Cys Leu Glu Val Leu His Leu Leu Cys
 20 25 30

<210> 154
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 154
 Met Cys Leu Ser Met Gln Pro His Gln Leu Pro Tyr Phe Ser Cys Leu
 1 5 10 15
 His Leu Ser Lys Thr Arg Ala Ala His Pro Ala Pro Pro Asp Phe Arg
 20 25 30
 Trp Gly Trp Ser Val Lys Thr Gln Ala Arg Arg Lys Thr Pro Ser Pro
 35 40 45
 Ser Lys Pro Ser Pro Arg Thr Arg Pro Met Cys Arg Pro Lys Ser Lys
 50 55 60
 Ala Arg Leu Ala Ala Lys Val Gln Ala Val Arg Lys Arg Arg Ser Gly
 65 70 75 80
 Asn Ser

<210> 155
 <211> 71
 <212> PRT
 <213> Homo sapiens

<400> 155
 Met Pro Gly Pro Ala Ala Ala Ser His Arg Ala Ser Thr Tyr Val Ser
 1 5 10 15
 Thr Trp Ser Cys Pro Pro His His Ser Trp His Ala Trp Gln Cys Thr
 20 25 30

Val Ala Arg Pro His Leu Gln Thr Ser His Cys Cys Thr Ser Gly Leu
 35 40 45
 Pro Leu Ala Asp Met Glu Ser Arg Leu Val Ala Ser Pro Ser Glu Trp
 50 55 60
 Asn Lys Leu Thr Trp Ala Gln
 65 70

<210> 156
 <211> 42
 <212> PRT
 <213> Homo sapiens

<400> 156
 Met Ile Ser Ser Ala Phe Leu Leu Leu Thr Leu Ile Arg Ser Tyr Leu
 1 5 10 15
 Leu Leu Arg Tyr Gln Asn Thr Thr Ser Met Thr Glu Leu Asp Pro Arg
 20 25 30
 Arg Leu His Cys Thr Ile Trp Met Glu Val
 35 40

<210> 157
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 157
 Met Ser Arg Ala Pro Gly Ile Leu Ala Ser Trp Arg Arg Ala Pro Ser
 1 5 10 15
 Leu Ser Val Gln Lys Gly Ser Gln Thr Ala Arg His Thr Cys His Pro
 20 25 30
 Glu Val Pro Leu Gly Asn Cys Phe Leu Pro Val Tyr Lys Ala Ser Pro
 35 40 45
 Leu Thr Val Thr Arg Leu Trp Ala Glu Arg
 50 55

<210> 158
 <211> 85
 <212> PRT
 <213> Homo sapiens

<400> 158
 Met Gln Arg Ala Leu Arg Arg Asp Thr Gly Gly Ser Gln Ser Asp Tyr
 1 5 10 15
 Pro Leu Ala Leu Ser Ser Phe Pro Thr Ala Gly Ser Ser Cys Pro Ala
 20 25 30
 Leu Gly Leu Thr Thr Pro Leu Ala Trp Arg Leu Cys Leu Ile Phe Ile
 35 40 45
 Thr Gly Arg Glu Thr Arg Ser Ile Pro Lys Glu Arg Glu Pro Arg Met
 50 55 60
 Pro Glu Arg Lys Ala Ser Pro Arg Arg Trp Asp Asn Phe Pro Tyr Lys
 65 70 75 80
 Val Trp Gln Ser Ser
 85

<210> 159
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 159
 Met Leu Leu Ala Asp Lys Glu Ala Ser Glu Ala Gly Leu Thr Asn Val
 1 5 10 15
 Pro Asn Asp Ala Asn Tyr Pro Arg Tyr Ser Pro Ala Glu Cys Leu Met
 20 25 30
 Ala Ile Gly Phe Gly Val Arg Lys Ser Arg Leu Glu His Leu His Leu
 35 40 45
 Gln Gln Cys Ala Gly Asp Phe Leu Ser Ala Ser Leu Ser Pro Thr Asn
 50 55 60
 Gln Ile Ser Val Ser Val Trp Ala His Ile His Lys Leu Ala Arg Gly
 65 70 75 80
 Asn Ser

<210> 160
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 160
 Met Gly Ala Ala Ala Lys Gly Ser Leu Trp Ala Ser Pro Phe Ser Arg
 1 5 10 15
 Ser Val Leu Pro Leu Cys Leu Gly Ser Ser Leu
 20 25

<210> 161
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 161
 Met Trp Asn Met Leu Ser Asp Ser Asn Tyr Gln Gln Phe Pro Ser Asp
 1 5 10 15
 Ser Ala Arg Val Leu Ser Phe Gly Ser Arg Val Leu Tyr Ser Lys Ser
 20 25 30
 Thr Ser Ser Phe Thr Leu Asn Ser Gln Asp Leu Tyr Ser Trp Thr Gln
 35 40 45
 Phe Val Thr Thr Thr Ile Phe Gln Ile Cys Ser His Lys His Pro Lys
 50 55 60
 His Pro Leu Lys Phe Tyr Thr Arg Ile Thr Glu Lys His Pro Ala Asp
 65 70 75 80
 Phe Leu Leu Ala Ala Ser Lys Glu Gln Leu
 85 90

<210> 162
 <211> 66
 <212> PRT
 <213> Homo sapiens

<400> 162
 Met His Cys Ala Val Cys Met Val Ser Phe Gln Pro Pro Pro Lys Trp
 1 5 10 15
 Phe Ser Pro Lys Ile Leu Lys Arg Asn Phe Met Phe Leu Cys Ile Phe
 20 25 30
 Thr Gly Ile Lys Glu Asp Gln Ile His Asn Phe Trp Gln His Cys Ser
 35 40 45
 Phe Pro Leu Pro Leu Ala Thr Ser Leu Trp Thr Trp Glu Thr Ser Leu
 50 55 60
 Trp Thr
 65

<210> 163
 <211> 75
 <212> PRT
 <213> Homo sapiens

<400> 163
 Met Thr Ser Arg Glu Asn Thr Asn Gly Ile Asn Ser Ala Val Ser Phe
 1 5 10 15
 Arg Ser Ser Leu His Arg Cys Phe Ser Lys Leu Met Phe Ser Glu Asn
 20 25 30
 Ser Arg His Arg Leu Arg Thr Asn Pro Pro Ser Pro Phe Arg Leu Gly
 35 40 45
 Trp Pro Met Gly Trp Ser Val Cys Val Leu Val Gly Pro Ala Val Tyr
 50 55 60
 Met Ser Ser Ser Ala Gln Arg Leu His Ser His
 65 70 75

<210> 164
 <211> 46
 <212> PRT
 <213> Homo sapiens

<400> 164
 Met Ile Leu Thr Thr Leu Met Tyr Gly Tyr Tyr Tyr Leu Asp Asp His
 1 5 10 15
 Ile Gly Phe Ala Phe Gly Thr Pro Arg Ser Leu Ser Leu Ser Ser Asp
 20 25 30
 Phe Leu His Ser Lys Gln Glu Gly Tyr Phe Ser Pro Thr Leu
 35 40 45

<210> 165
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 165
 Met Ser Ser Val Gly Ser Thr Glu Ala Gly Arg Ser Glu Gln Ala Glu
 1 5 10 15
 Arg Gly Ile Gly Val Ser Glu Arg Val Gly Val Gln Ala Gln Asp Arg
 20 25 30
 Thr Glu Leu Ser Ala Asp Cys Asn Thr Val Thr Pro Lys Val Lys Ala
 35 40 45

Ser

<210> 166
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 166
 Met Val His Arg Pro His Ile Ser Leu Gln Leu Asn Phe Gly Pro Lys
 1 5 10 15
 Arg Ser Arg Leu His Thr Phe Arg Asn Lys Ser Tyr Ser Ser Ala Gln
 20 25 30
 Asn Gly Ser Thr Arg Leu Asp Leu Pro Thr Arg Pro Ala Trp Pro Leu
 35 40 45
 Arg Leu Gln Arg Val Ala Leu Asp
 50 55

<210> 167
 <211> 8
 <212> PRT
 <213> Homo sapiens

<400> 167
 Met Met Arg Lys Ser Leu Pro His
 1 5

<210> 168
 <211> 2067
 <212> DNA
 <213> Homo sapiens

<400> 168
 ggaggcagag ctctgggaat ctcaccatgg cctggacccc tctcctgctc cccctcctca 60
 ctttctgcac agtctctgag gcctcctatg agttgacaca gccaccctcg gtgtcagtgt 120
 ccccaggaca aacggccacg atcacctgct ctggagatgc attgccaaaa aaaacatcct 180
 tattggtacc agcagaagtc aggccaggcc cctgtactgg tcatctatga ggacaacaaa 240
 cgaccctccg ggatccctgc agagattctc tgctccagc tcagggacaa tggccacctt 300
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<210> 169

<211> 1692

<212> DNA

<213> Homo sapiens

<400> 169

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<210> 170

<211> 949

<212> DNA

<213> Homo sapiens

<400> 170

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<210> 171

<211> 2331

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (2331)

<223> n = a,t,c or g

<400> 171

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<210> 172

<211> 416

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(416)

<223> n = a,t,c or g

<400> 172

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<210> 173

<211> 1737

<212> DNA

<213> Homo sapiens

<400> 173

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<210> 174
 <211> 6464
 <212> DNA
 <213> Homo sapiens

<400> 174
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<211> 906

<212> DNA

<213> Homo sapiens

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<212> DNA

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<212> DNA

<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <213> Homo sapiens

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 <211> 749
 <212> DNA
 <213> Homo sapiens

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 <211> 723
 <212> DNA
 <213> Homo sapiens

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aagatctctt	ctggtagtgc	acccttcccc	aaggccagg	aaaagtctgt	atgaccttcc	600
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agg

723

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 <211> 1572
 <212> DNA
 <213> Homo sapiens

<400> 216
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 gcgagccatt ctccggaccc cagcgaatac ttttaggaagc acccacctgt tcgcagatca 180
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 <211> 719
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (1)...(719)
 <223> n = a,t,c or g

<400> 217
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 aagttccatt attataaagt ataactatc ttaacacacc catggtacag tatatatata 660

aaaaaacttg ctgaacacag gatgcattaa gaattcaaca acttaagaac acatatcctt 719

<210> 218
 <211> 1755
 <212> DNA
 <213> Homo sapiens

<400> 218
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 <211> 1437
 <212> DNA
 <213> Homo sapiens

<400> 219
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<210> 220
 <211> 357
 <212> DNA
 <213> Homo sapiens

<400> 220						
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<210> 221
 <211> 339
 <212> DNA
 <213> Homo sapiens

<400> 221						
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 <212> DNA
 <213> Homo sapiens

<400> 222						
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<210> 223
 <211> 2086
 <212> DNA
 <213> Homo sapiens

<400> 223						
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catgaccttt	tgggttttaa	atggcagcat	agcccagtg	tcaagggcat	agcttgggtg	1980
cagctgtgtc	ctctcagtga	gtcctcaact	tcctcgttgc	ttcagctgga	agatgcagag	2040
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<210> 224

<211> 942

<212> DNA

<213> Homo sapiens

<400> 224

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gggggctttc	gcaacattgc	aatccaaact	tccccagtc	tcaggaaagca	tttcccagtt	180
ttcaaaagga	agagactcac	agccagtaag	tccgtggagg	aaatgccaac	agcctcccaa	240
agtgccatcc	atgtcaacgg	taacctctct	gaacaggaca	ttgtgtcttc	tgaccttgcc	300
tacttaaggt	tggctcagca	tcttgaggat	gggcctcgaa	gggtcaaggt	gtcccatgca	360
ttcctcccaa	gggtccccaa	ggtgcaaac	aatggctcctg	ttagcatatg	cttggaagca	420
ggaacttgga	ggtccttaga	gaaagccaca	gctgccattc	aggttccaga	tgatatttat	480
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aacagcctca	caggccatc	tgacctggg	ctgtctctcc	agcctcagct	tctgccact	600
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tggctctccc	ctgaagtgg	accactcgcc	agccccggct	ctcccctgat	agcctgggccc	900
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<210> 225

<211> 1528

<212> DNA

<213> Homo sapiens

<400> 225

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cttgatgaac	ccattgaaaa	tcccctcttt	tgtttctcaa	gcttttagcaa	tgaccttgca	180
atattgcttc	caaaagtgtt	ccttaagaat	attcatatac	tgcaattcat	ctacaggagt	240
tttcaccttt	tgacaatggc	aaaagcaaa	tttgaagggtg	ctgagtctgt	ggagccagtg	300
tcaccttcac	agcccaaaa	gccatcctat	gtccccctag	aagagctatg	gacgaggtta	360
acaaaaggga	acagcaggcc	tcagcagagg	gacagggaga	agggaggatg	gatgaaggga	420
gtgcagcaag	gccatcaagg	agtaggaaa	caggaggaa	gttcagagaa	catcaaagaa	480
aaagctggga	ttgttgcctg	tgagggtcct	aacaacaagt	tagataaatt	catgggaatc	540
ctttcttggga	aagacagcaa	gcattccctc	aacaatgaga	agataatcct	gagaggctgc	600
atcctgagaa	ataccagctg	gtgttttggga	atggttat	ttgcaggctc	tgacactaaa	660
ctaattgcaga	atagtggtaa	gacaaagt	aaaaggacaa	gcattgatag	attgatgaat	720
actctagtac	tatggattat	gctaatttct	caaccagtg	tagaatttat	catgagagga	780
cacagttatt	ttataaactg	ggaccggaag	atgtattatt	ctcgaaaagc	aatacctgca	840
gtggctcgaa	cgaccagct	caatgaggaa	ctggggcaga	ttgagtacat	tttctccgac	900
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aatgataaag ggaatatcac cactgacctc gcagaaacac aaactaccat cagagaatac 1140
tataaacacc tctacactaa taaactagaa aacctagaag aaatggataa attcctggat 1200
gcatacacct tatcaagact aaaccaggaa gaagttgaat ccttgagtag accaataaca 1260
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agattcacag ctgaattgta ccagaaatac aaggaggagc tggaaaaaga gcctgtggat 1380
ttctcagtca aatctcaagc ggatagagaa tttcagttct ttgaccacaa tctgatggaa 1440
tccattaaaa tgggtgatcc caaagttcat gaattcctta ggttacttgc tctctgccac 1500
actgtaatgt cagaagagaa tagcgacg 1528

```

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<210> 226
<211> 515
<212> DNA
<213> Homo sapiens

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<400> 226
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tgtaggcaat tctgacaccg agctccccggg ctcggttggc agaagatcgc tttgggaatc 180
ctcctactct acgaggacca gaaaccaagg acgccaagcc atacaaattc agcacagctg 240
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ttgccagcca gaataactgt gagagatgca agcatagtcc tggaaacaaa cagcacaaat 360
cctttaaagc cctaaaggat gaagatcttc ctgtagagaa gtatttaatg gaaaggcagc 420
ctgtaggtga gccagctgcc gaccaggtag ctatggatgt gatgcacagc cccatcctcc 480
aactggaag gaaacacaaa gtctcaagtg acagc 515

```

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<210> 227
<211> 1023
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1) ... (1023)
<223> n = a,t,c or g

```

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<400> 227
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caaacagaaa acttgggtgt tgtttattat gtcaacaagg acttcaaaaa tgaatataaa 180
ggaatgttat tacaaaaggt agaaaagagt gtggaggaag attatgtgac taatatcgga 240
aataactgct ggaagaaaag acaacaaang gcaattaggc aggagaagga aataaagggt 300
attcaattag gaaaagagga agtcaaattg tcctgtttg cagatgacat gattttatat 360
ctagaaaaac ccattgtctc agcccaaaat ctcttaagc tgataagcaa cttcagcaaa 420
gtctcaggat acaaaatcaa tgtacaaaaa tcacaagcat tcttatacac taacaataga 480
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tacctaggaa tccaacttac aagggatgtg aaggacctct tcaaggagaa ctacaaacta 600
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ggaagaatca atatgtgaa aatggccata ctgcccaagg taatttacgg attcaatgcc 720
atccccatca agctaccaat gattttcttc acagaattgg aaaaaactac ttcaaagttc 780
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ggaggcatca caccacctga cttcaaaactg tactacaagg ctacagtaac caaacagca 900
tggactagaa aaatttatc agctaagaaa cgtaagtc aaatttcagt ggaacctgtt 960
tacagcgggtg tgacactaac tacagcaata cagcttgctc ctcttctgtg cacagctctg 1020
taa 1023

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<210> 228
 <211> 936
 <212> DNA
 <213> Homo sapiens

<400> 228
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 ctcggtctag tggatgatgc tttccaaccc aaaaacatcc aggaatccat tgtggcaaat 120
 gtggtttcag cagctcggag gaaggtgctt ccagggcctc cagaggattg gaatgaaaga 180
 ctgtcctata ttccctcaaac ccagaaggcc tatatgggct catgtggaag gcaagagtat 240
 aatgtcacag ccaataataa tatgtccacc acctcccaat atggttcaca gttgccatat 300
 gcatattata ggcaggcttc aagaaatgat tctgcaatca tgtccatgga aaccaggcac 360
 ttgtacactc gccagcttta ctgttacagc tttggagact ctggaaactt ctgtgaaaat 420
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 acttccatac catccagtgg aataagttag gctttgatat ctgaaaatga aaacaaaaac 540
 ctcagacatc tcacacatgg gggttatgtg gaaagtacca ccctgcagat tgcaccggcc 600
 acaaagaccc agtgcacaga attcttcctc gccctgttca agactgaagt tcccctagct 660
 gagaaccaa gaagtgggtc cgactgtgca ggcagcttga aagaagaaac aggcccgagc 720
 taccaaaggg ctcccaaat gcctgactcc caaagaggac gcgtggcaga agagctgac 780
 ttaagggaga aagtagaagc gagtactcag aacaattact atgtagggtga gctgacaggt 840
 gtaaccttac aaaatggtta tggagaaaaa cccatccttg ctactcaagg tgaggctcac 900
 agaccatcag caatggaatc acctggaggc ttgtga 936

<210> 229
 <211> 1448
 <212> DNA
 <213> Homo sapiens

<400> 229
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 attgcttact atgtgtcagg cggtgtacta ggcactgggg aaaactgtaa ataaaaagaga 120
 cccagttcct tccttttttt cagggttcag tctatcagga aaggcagaca tttaaaaagg 180
 gtcttgtgag gactgttatg aaacagggaag tacgagtgcc atttctatac cttagtaciaa 240
 tcaactcggtt taattcacat ctcccatggt ggcaagtttg cctcagtgtc agccgggtcaa 300
 ttgccactca aggggatcag aacatttatg tatctggaat gcttgaatat ttaagagaaa 360
 accttttttg ccgctttgat aatgataatt tttgtctatt gaatgggtgat gctgtgattt 420
 tcaggatgta tgtatcatgg aaactggtag agaaagaaag aactgagatc atgctgaagt 480
 atactggggc ccaccaagag gtagagctga gtgcaccaat tgtcaccaaa atggcaacc 540
 aatatttaag agaaaacctt tttggccgct ttgataatga taatttttgt ctattgaatg 600
 gtgatgctgt gatttttcagg atgtatgtat catggaaact ggtagagaaa gaaagaactg 660
 agatcatgct gaagtacact gggggccacc aagagacttg gttaaaagac cttgagggaat 720
 ccccccttta cgaagcctta tccatgagag gacaagataa ggagaccctt ggtttgtgga 780
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 aggtcaaagg cacaaccttc gtcacacact cagtccctgc tggcaagag aaagacgagg 1380
 agcgtggaat cggagacctg gagcatgcga gggacttgag aaattcacca actcccttgt 1440
 ttactga 1448

<210> 230
 <211> 906

<212> DNA

<213> Homo sapiens

<400> 230

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acaagggatg	tgaaggactt	cttcaaggag	aactacaaac	cactgctcaa	tgaaataaaa	120
gaggaaacaa	acaaatggaa	gaacattcca	tgctcatggg	taggaagaat	caatatcgtg	180
aaaatggcca	tactgcccc	gagggtgcct	catggttttc	tgccaaatat	gaaacttgaa	240
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gtccatcccc	ctgtgtcagg	tttgatcttc	agctcctcca	gaaccctgct	ttcctttatg	480
ggaattatga	gagaagactt	aggggttttc	aggaggcaga	tcctccattt	ccccatggct	540
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agtcagtata	ctccatttag	tagatgtgat	aatgcattct	acaaagaaaa	tgtgtttcta	840
caaaagctgg	agagaaacac	accagatatt	gcagaaagat	ttgactgttt	attactgaca	900
tattag						906

<210> 231

<211> 1117

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1117)

<223> n = a,t,c or g

<400> 231

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aaagagagaa	aagagaaaag	aagaaaagag	acatgagagg	agaggagagg	tgagaaaaga	180
gagaagagag	aaaagaaaag	gagaaggag	ggaaggatgt	ccatatcttt	tgcgaggagg	240
tacagcatac	tctagagcac	gggtccccag	tccccaggcc	acgaaccggt	acagctctga	300
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tgccctaacy	tcttccatta	tggagctggg	gccaggtgtc	agcaaactgg	ttcagtggca	1080
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<210> 232

<211> 4707

<212> DNA

<213> Homo sapiens

<400> 232						
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<213> Homo sapiens

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<210> 237

<211> 1353

<212> DNA

<213> Homo sapiens

<220>
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 <222> (1) ... (1353)
 <223> n = a,t,c or g

<400> 237

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tcctgtgcc	ttgtggtagg	taacacacat	tccttcattt	acacaggggt	catagccatc	180
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<210> 238
 <211> 362
 <212> DNA
 <213> Homo sapiens

<400> 238

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gcacagtggc	cagacctcac	ttgcagacct	ctcattgtctg	cacatctggc	ttgcctctgg	300
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ag						362

<210> 239
 <211> 1350
 <212> DNA
 <213> Homo sapiens

<400> 239

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atagatggga	tgtgaagact	tccaggctgt	tgacaccagg	ctcagattac	tttgtctatt	360
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<210> 240
 <211> 618
 <212> DNA
 <213> Homo sapiens

<400> 240						
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agttgctcag	tgggaagagc	aagtgaccag	cagagtccgt	caccaccctc	ccctcttacc	240
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gtgaaagaac	agggagtga	gaacattttt	ggtaagtcaa	ctctggggat	gtcgctgcat	360
gtctccagct	cagtcttttag	aaggtatata	ttacctgggt	accagccaag	aggtcacaca	420
gtcatggtgt	cacaggtaaa	cattgacttc	cagacccgag	aagccacgag	gaagaacctg	480
caggagccat	ccctgacttg	ctttgaccaa	gcccaggaa	aagtacacag	cctcatggag	540
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<210> 241
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 241						
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ctgacagcag	ggggcgccaa	tgtctgggaa	aaatctacct	gccgcaaaaa	atccagacaa	300
ttggtgctga	ggaatgtaaa	ggttccaggg	aaaagcccat	gtggtgaaat	gctgcccata	360
ctcaaaaaaa	accagttaaa	catccttctc	ttgcaaccag	tggacacaga	gactttggaa	420
gggcctccag	gccttggcct	ggatgcagag	ggccttgaga	agagacacag	ctggatcctc	480
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aggaaggga	actcgctcca	tccccaagga	aagagaacca	aggatgccag	aaaggaaagc	600
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gggacctag						669

<210> 242
 <211> 2043

<212> DNA

<213> Homo sapiens

<400> 242

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accaagtcaa acctaagcca aaagaacaaa gctggaggca tcacgctacc tgacttcaaa      180
ctatactaca aggctacagt aacaaaaaca gcatggtagt ggtaccacaaa cagagatata      240
gatcaatgga acagaacaga gccctcagaa ataatgccgc atatctacaa ctatctgac      300
tttgacaaa ctgagaaaaa caagcaatgg ggaaaggatt ccctatttaa taaacggttc      360
tgggaaaaact ggctagccat atttagaaag ctgaaactgg atcccttcct tacaccttat      420
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aagagcttct gcacagcaaa agaaactacc atcagagtga acaggcaacc tacaaaaagg      660
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ctcaaaaaaa ttcacaagaa aaaaacaaac aaccccatca gaaagtgggc gaaggatatg      780
aacagacact tctcaaaaaga agacatttat gcagccaaaa aacacatgaa aaaatgctca      840
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gttagaatgg caatcattca aaagtcagga aacaacagag ttttaccctc tgcacctctg      960
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agtgtggtaa agctaaaagc tggcttcaca atcggaaaag ttcacaatac agaagtaaca     1860
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gttgtgacct acccaacaaa cttggaaaat gtgatacggc atccgccaga ggctctggct     1980
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<210> 243

<211> 1116

<212> DNA

<213> Homo sapiens

<400> 243

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gaaatgagga ccaaggacca gccagatggc agcagtctga gtccagctca gagtccagc     240
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gggacctga actttctaga cagcagtcct caggtccgtt accatccaag gaactctggg     780
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ggggacgaca	cagtgtctgtc	accacggcca	gcctgggtcca	agctagcagc	tacgaggagt	900
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gaccccttgg	ctgccgcgcc	catctcagca	gcgggcagcc	gcagaggagc	cctggcctcc	1020
tggtttgct	ctcccacacg	ctcccagaac	ccggcccgac	ccccacgcc	agactgtaga	1080
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<210> 244
 <211> 413
 <212> DNA
 <213> Homo sapiens

<400> 244						
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ctgctctcac	aaacacccaa	agcatccttt	gaagttttac	accagaatca	ctgaaaagca	360
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<210> 245
 <211> 975
 <212> DNA
 <213> Homo sapiens

<400> 245						
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<210> 246
 <211> 349
 <212> DNA
 <213> Homo sapiens

<400> 246						
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349

<210> 247
<211> 431
<212> DNA
<213> Homo sapiens

<400> 247
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taagattcag ctctactcc tcctcctctg gtccagtcac tctggctctcc ttccattccc 180
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<210> 248
<211> 1272
<212> DNA
<213> Homo sapiens

<400> 248
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<210> 249
<211> 380
<212> DNA
<213> Homo sapiens

<400> 249
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cccatccac aacatactca gcccagcct ttaaaactgg ggcttatgct tgagtagtga 180

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<210> 250
 <211> 560
 <212> DNA
 <213> Homo sapiens

<400> 250						
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gttttaccac	agcacatgcg	cagtacagga	tctgtctgtt	cgtttgcgg	cgctaccaat	180
aaagttttag	tgagcacaga	ctcccttttc	tttgccaaga	tggcggagta	cgacttgact	240
actgcacatcg	cgcaactttt	ggatcgccat	ctagtctttc	cgcttcttga	atttctctct	300
gtaaaggagg	tgaggggggc	tttggggcgca	aggaaggcgt	ggggggcgat	gaggtgctga	360
gcaaggccga	aaggtgggtg	ctgtagtcct	aggcctgaca	cgtgcgaggc	ggtcgcgagt	420
ttggttccctg	gacggacact	aaggatcttc	tggtagttta	gcgtcgtctc	agttaagaag	480
caccgcaaaa	tgcagtttagc	tctctgttct	gcactctgtg	attcagccaa	ctgcagattg	540
aaaatattca	gggaaagaaa					560

<210> 251
 <211> 1092
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(1092)
 <223> n = a,t,c or g

<400> 251						
cagtacgacg	tttaaacacg	gccatgcaag	caaaattacc	ccactaaagg	aataagttcg	60
gcccaccttt	tttttttttt	ttttgctgct	ggaacgtttt	attaagttaa	gaggttcagg	120
gagcagaaga	gaaacacett	ttgggtggct	tctggcggtt	ctgcacccaa	gcacagcctc	180
gaaggaggct	gtggggccat	ggaggcccag	ctgctagctc	cctctgtcct	gagccccatg	240
gtacgggtcc	aaatggggca	ggaagtgtta	gtaggaggta	gggcaggaag	aggggtngca	300
ggctcccgcc	tctcccctgt	agagacaccg	ccgccatggc	ttgctgcctg	ggcctccgcc	360
agacctctgg	gccagggcca	ccagctcaga	agcccaagca	cagcgggtggc	tggagacaga	420
gggggaccag	ggttggaggc	acacagccac	caggaattgc	tttttttttt	ttttttttta	480
aagtataaag	tgttttggaa	aaaaaggaaa	aaaactata	taaaaatctc	ttcacatata	540
aaatcctgaa	gaaggtgcaa	ggtgagaccc	cagntgcgag	gggcgcgcat	cagatatgca	600
gtgtgtgtgt	gtgtgtgtgt	gtgtgtgtat	ccgtgtgtac	atgtgtgcac	gtgtgtgcgt	660
atgtgtctgt	gtgtctgtgt	gtgtgtgtgt	gtgtgtgtgt	gtgtgtgtgg	tgggtgcaag	720
tgcacgtgtg	gcccacaga	gggtggggag	aaagcttggc	tttttacttc	catccaggag	780
ggaaggagg	gcggctggtc	ctccagcctg	agagggtctg	cagctggggc	ggacctctac	840
tcagccaggc	tgttttgcga	tcgactcctt	ctcctggagg	gccggccatg	gcaagacgca	900
gggtgctcct	cagctgctcg	aatctcccg	tcagagccgt	ggtcttgatg	gtggctcagc	960
tcacataga	acgtcctggg	actttcccg	gggtgaagcg	ttgtccttct	gcacatctctg	1020
gagctcgtcc	cggaggcacc	tgccctactt	tcttaagtac	tggagttccg	tttcttttaa	1080
ccgaaaccac	ac					1092

<210> 252
 <211> 246
 <212> PRT

<213> Homo sapiens

<400> 252

```

Arg Gln Ser Ser Gly Asn Leu Thr Met Ala Trp Thr Pro Leu Leu Leu
 1          5          10          15
Pro Leu Leu Thr Phe Cys Thr Val Ser Glu Ala Ser Tyr Glu Leu Thr
          20          25          30
Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Thr Ile Thr
          35          40          45
Cys Ser Gly Asp Ala Leu Pro Lys Lys His Pro Tyr Trp Tyr Gln Gln
          50          55          60
Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr Glu Asp Asn Lys Arg
          65          70          75          80
Pro Ser Gly Ile Pro Glu Arg Phe Ser Ala Ser Ser Ser Gly Thr Met
          85          90          95
Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu Asp Glu Ala Asp Tyr
          100          105          110
Tyr Cys Tyr Ser Thr Asp Ser Ser Gly Asn His Arg Gly Val Phe Gly
          115          120          125
Gly Gly Thr Arg Leu Thr Val Leu Ser Gln Pro Lys Ala Ala Pro Ser
          130          135          140
Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala
          145          150          155          160
Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val
          165          170          175
Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr
          180          185          190
Thr Pro Gly Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
          195          200          205
Ser Leu Thr Pro Glu Gln Trp Lys Ser His Lys Ser Tyr Ser Cys Gln
          210          215          220
Val Thr His Glu Gly Ser Thr Val Glu Glu Thr Gly Ala Pro Thr Glu
          225          230          235          240
Tyr Leu Leu Arg Val Tyr
          245

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<210> 253

<211> 539

<212> PRT

<213> Homo sapiens

<400> 253

```

Met Glu Lys Gly Ser Gly Phe Ile Lys Tyr Ser Thr Tyr Lys Gln Gly
 1          5          10          15
Thr Ile Arg Val Ala Glu Glu Ala Glu Thr Ala His Ser Ser Val Leu
          20          25          30
Ile Gly Pro Glu Lys Gly Val Val His Leu Ala Thr Ala Ala Val Leu
          35          40          45
Asn Ala Val Trp Asp Leu Trp Ala Lys Gln Glu Gly Lys Val Leu Ala
          50          55          60
Val Gly Arg Glu Leu Gln Glu Glu Lys Glu Glu Thr Gly Trp Arg
          65          70          75          80
Lys Ala Gln Ala Ala Val Glu Gly Gly Val Gly Thr Trp Trp Leu Thr
          85          90          95
Ala Ser Ile Arg Ala Ala Asn Ala Phe Thr Val Arg Lys Lys Trp Gly
          100          105          110
Leu Tyr Thr Tyr Val Leu Gln Ile Leu Ser Phe Leu Leu Gln Ala Cys
          115          120          125
Leu Glu Val Thr Cys Gly His Asp Leu Ile Met Gly Cys Ile Lys Ser
          130          135          140

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Lys Glu Asn Lys Ser Pro Ala Ile Lys Tyr Arg Pro Glu Asn Thr Pro
145          150          155          160
Glu Pro Val Ser Thr Ser Val Ser His Tyr Gly Ala Glu Pro Thr Thr
          165          170          175
Val Ser Pro Cys Pro Ser Ser Ser Ala Lys Gly Thr Ala Val Asn Phe
          180          185          190
Ser Ser Leu Ser Met Thr Pro Phe Gly Gly Ser Ser Gly Val Thr Pro
          195          200          205
Phe Gly Gly Ala Ser Ser Ser Phe Ser Val Val Pro Ser Ser Tyr Pro
          210          215          220
Ala Gly Leu Thr Gly Gly Val Thr Ile Phe Val Ala Leu Tyr Asp Tyr
225          230          235          240
Glu Ala Arg Thr Thr Glu Asp Leu Ser Phe Lys Lys Gly Glu Arg Phe
          245          250          255
Gln Ile Ile Asn Asn Thr Pro Met Val Leu Asn Leu Gly Gln Asn His
          260          265          270
Pro Gly Asp Ile Trp Gln Tyr Leu Glu Thr Phe Leu Val Thr Val
          275          280          285
Gly Val Leu Pro Leu Ser Ser Ser Ala Ser Thr Pro Val Phe Asp Arg
          290          295          300
Val Thr Asn Gly Val Thr Pro Thr Ile Lys Asp Leu Thr Gly Cys Cys
305          310          315          320
Val Glu Asn Arg Leu Leu Thr Ser Asn Ser Ser Asp Phe Phe Thr Leu
          325          330          335
Ile Asn His Ser Asn Ser Ser Lys Thr Pro Phe Gln Asn Thr Arg Leu
          340          345          350
Val Val Ser Arg Gly Asn Ser Ser Glu Lys Gln Phe Ala Ile Arg Phe
          355          360          365
Gln Asp Gly Lys Thr Asp His Ala Ile Gln Leu Ser Ser Gly Lys Lys
          370          375          380
Thr Ala Leu Gly Arg Glu Ala Leu Glu His Pro Glu Ser Leu Asp Ser
385          390          395          400
Arg Lys Val Gly Gln Arg Ser Arg Trp Ser Ser Gln Ala Ala Ser Pro
          405          410          415
Ile Ser Gly Pro Ile Gln Ala Glu Thr Ala Leu Leu Cys Pro Gly Asp
          420          425          430
Gln Trp Thr Gln Glu Phe His Thr Ser Pro Leu Leu Thr Val Pro His
          435          440          445
Leu Pro Asp Ile Tyr Thr Leu Asp Cys Cys Arg Lys Asp Phe Ser Ile
          450          455          460
Tyr Ile His Ser Phe Gly Asp Ile Thr Gln Ser Tyr Ile Phe Lys Tyr
465          470          475          480
His Leu Gln Ile Asp Asp Tyr Gln Leu Cys Ala Gln Ala Leu Lys Asp
          485          490          495
Gly Trp Thr Arg Pro Pro Pro Phe His Thr Ala His Leu His Phe Ser
          500          505          510
Leu Leu Thr Leu Ala Cys Ala Glu Thr Val Thr Ser Ala Glu Thr Pro
          515          520          525
Asp Ala Leu Ala Lys Ser Arg Phe Lys Val Lys
          530          535

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<210> 254

<211> 236

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (236)

<223> Xaa = X or * as defined in Table 6

<400> 254
 Gly Thr Arg Asp Ala Thr Ala Glu Glu Asn Arg Val Leu Leu Ala Met
 1 5 10 15
 Val Asn Pro Thr Val Phe Phe Asp Ile Ala Val Asp Gly Glu Pro Leu
 20 25 30
 Gly Arg Val Ser Phe Glu Val Arg Gly Leu Asp Thr Lys Lys Xaa Leu
 35 40 45
 Leu Ile Xaa Ser Ile Lys Leu Cys Xaa Gln Ile Gly Gly Ser Ser Ile
 50 55 60
 Phe Ile Thr Ser Asp Xaa Lys Asn Ser Cys Leu Pro Leu Ile Val Gln
 65 70 75 80
 Gln Cys Leu Leu Phe Leu Arg Ile Leu Pro Leu Phe Ala Asp Lys Val
 85 90 95
 Pro Lys Thr Ala Glu Asn Phe Arg Ala Leu Ser Thr Gly Glu Lys Gly
 100 105 110
 Phe Gly Leu Xaa Gly Val Pro Cys Phe His Arg Ile Ile Pro Gly Phe
 115 120 125
 Met Cys Gln Gly Gly Asp Cys Glu Arg His His Asn Gly Thr Gly Gly
 130 135 140
 Lys Ser Ile Tyr Thr Glu Lys Phe Glu Asp Glu Asn Phe Ile Leu Lys
 145 150 155 160
 Ala Tyr Gly Val Leu Gly Ser Leu Ser Met Ala Asn Ala Gly Pro Asn
 165 170 175
 Thr Asn Gly Ser Gln Phe Phe Ile Cys Thr Ala Lys Thr Glu Trp Leu
 180 185 190
 Asp Gly Lys Pro Val Val Phe Gly Lys Val Lys Glu Gly Met Asn Ile
 195 200 205
 Val Glu Ala Met Glu Arg Phe Gly Ser Arg Asn Gly Lys Thr Ser Lys
 210 215 220
 Lys Ile Ile Ser Ile Ala Asp Cys Gly Gln Leu Glu
 225 230 235

<210> 255

<211> 105

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(105)

<223> Xaa = X or * as defined in Table 6

<400> 255
 Ile Cys His Gln Pro Thr Ser Leu Ser His Gln Xaa Glu Arg Asn Gly
 1 5 10 15
 Trp Pro Gly Arg Trp His Ser Gln Pro Arg Ser Lys Phe Cys Arg Leu
 20 25 30
 Arg Val Leu Ser Gln Gly Asp His Glu Lys Lys Ser Leu Pro Ser Gly
 35 40 45
 Gln Arg Pro His Arg Thr Gly Cys Ala Ser Ser Ser Gly Ser Ser Lys
 50 55 60
 Gly Leu Leu Leu Leu Pro Leu Asp Gly Leu Gly Val Ile Val Leu Ile
 65 70 75 80
 Asn Pro His Leu Val Val Phe Pro Gly Met Arg Ala Pro Xaa Leu Leu
 85 90 95
 Pro Arg Leu Trp Leu Arg Arg Trp Ser
 100 105

<210> 256

<211> 128
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(128)
 <223> Xaa = X or * as defined in Table 6

<400> 256
 Val Arg Asp Tyr Asn Leu Thr Glu Glu Gln Lys Ala Ile Lys Ala Lys
 1 5 10 15
 Tyr Pro Pro Val Asn Arg Lys Tyr Glu Tyr Leu Asp His Thr Ala Asp
 20 25 30
 Val Gln Trp Ile Val Leu His Arg Ala Xaa Ile Tyr Phe Phe Arg Leu
 35 40 45
 His Ala Trp Gly Asp Thr Leu Glu Glu Ala Phe Glu Gln Cys Ala Met
 50 55 60
 Ala Met Phe Gly Tyr Met Thr Asp Thr Gly Thr Val Glu Pro Leu Gln
 65 70 75 80
 Thr Val Glu Val Glu Thr Gln Gly Trp Gly Glu Glu Phe Ser Leu Ser
 85 90 95
 Lys His Pro Gln Gly Thr Glu Val Lys Ala Ile Thr Tyr Ser Ala Met
 100 105 110
 Gln Val Tyr Asn Glu Glu Asn Pro Glu Val Phe Val Ile Ile Asp Ile
 115 120 125

<210> 257
 <211> 111
 <212> PRT
 <213> Homo sapiens

<400> 257
 Val Thr Ser Ser Cys Pro Arg Lys Lys Arg Arg Phe Gly Gly Asp Arg
 1 5 10 15
 Pro Ser Ser Ser Phe Ser Pro Pro Ser Lys Glu Leu Leu Ala Val Lys
 20 25 30
 Ala Pro Arg Glu Gly Arg Arg Gly Pro Gly Asn Glu Ser Arg Ser Glu
 35 40 45
 Pro Ser Gln Pro Leu Asp Ser His Gly Pro Gly Leu Arg Arg Thr Phe
 50 55 60
 Leu Pro Pro Ser Pro Arg His Pro Thr Lys Asp Arg Arg Thr Ala Ala
 65 70 75 80
 Arg Ser Gly Pro Arg Arg Lys Arg Gly Gln Thr Asn Glu Ile Arg Gly
 85 90 95
 Cys Lys Glu Glu Gly Glu Lys Tyr Leu Val Pro Ala Gln Gly
 100 105 110

<210> 258
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 258
 Phe Tyr Phe Val Pro Ser Gln Glu Ser Val Pro Ser Ala Ser Pro Thr

```

      1           5           10           15
Gly Ile Pro Lys His Ser Leu Arg Lys Thr Thr Ser Thr Glu Glu Pro
      20           25           30
Arg Gly Thr His Ser Gln Gly Gln Phe Thr Met Pro Leu Ala Gly Met
      35           40           45
Ser Leu Gly Ser Leu Lys Ser Glu Phe Val Pro Leu Phe Ser Ala Thr
      50           55           60
Pro Phe Trp Val Pro Phe Ser Ser Leu Pro Leu Phe Pro Trp Val Leu
      65           70           75           80
Val Glu Asp His Val Cys Leu Leu Asp Cys Val Val Val Asp Leu Gln
      85           90           95
Asp Met Asp Ile Phe Ala Ala Glu Arg His Pro Arg Asp Tyr Ser Lys
      100          105          110
Ala Pro Glu Asp Ser Ser Gly Asp Leu Ile Phe Pro Ser Tyr Phe Val
      115          120          125
Arg Gln Thr Gly Gly Ser Leu Leu Thr Glu Pro Cys Arg Leu Lys Leu
      130          135          140
Gln Val Glu Arg Asn Leu Asp Lys Glu Ile Ser His Thr Val Pro Asp
      145          150          155          160
Ile Ser Ile His Gly Asn Leu Ser Ser Val His Cys Ser Leu Asp Leu
      165          170          175
Tyr Lys Tyr Lys Leu Ile Arg Gly Leu Leu Glu Asn Asn Leu Gly Glu
      180          185          190
Pro Ile Glu Phe Met Arg Pro Tyr Asp Leu Gln Arg Ser Lys Asn
      195          200          205
Ser Tyr Cys Pro Glu Trp Arg Ser Val His Leu Tyr Val Leu Pro His
      210          215          220

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<210> 259
<211> 164
<212> PRT
<213> Homo sapiens

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      <400> 259
Met Ile Val Asn Leu Phe Asn Met Phe Ile Thr Tyr Gly Asp Thr Phe
      1           5           10           15
Leu Pro Thr Pro Ser Ser Tyr Asp Glu Leu Tyr Tyr Glu Ile Ile Arg
      20           25           30
Met His Gln Ser Phe Asp Asn Leu Tyr Ser Met Val Leu Arg Leu Ser
      35           40           45
Thr Asn Ala Gly Gln Trp Lys Glu Ala Ala Ser Lys Val Thr His Ala
      50           55           60
Leu Val Asn Ile Arg Ala Ile Ile Asn His Phe Asn Pro Lys Ile Glu
      65           70           75           80
Ser Tyr Ala Ala Val Asn His Ile Ser Gln Leu Ser Glu Glu Gln Val
      85           90           95
Leu Glu Val Val Arg Ala Asn Tyr Asp Thr Leu Thr Leu Lys Leu Gln
      100          105          110
Asp Gly Leu Asp Gln Tyr Glu Arg Tyr Ser Glu Gln His Lys Glu Ala
      115          120          125
Ala Phe Phe Lys Glu Leu Val Arg Ser Ile Ser Thr Asn Val Arg Arg
      130          135          140
Asn Leu Ala Phe His Thr Leu Ser Gln Glu Val Leu Leu Lys Glu Phe
      145          150          155          160
Ser Thr Ile Ser

```

<210> 260
 <211> 815
 <212> PRT
 <213> Homo sapiens

<400> 260
 Met Thr Pro Gly Gln Leu Ser Asn Val Arg Ala Pro Gly Ser Ala Glu
 1 5 10 15
 Lys Gly Ser Gly Asp Thr Gly Asp Ala Arg Pro Pro Ser Ala Ala Pro
 20 25 30
 Pro Gly Gly Ser Ala Gly Glu Ala Arg Thr Ala Gly Ala Arg Tyr Leu
 35 40 45
 Cys Pro Arg Ser Ser Leu Ser Gly Gly Ala Ala Ala Thr Arg Thr Cys
 50 55 60
 Gly Leu Ala Asn Pro Glu Glu Gly Pro Ser Ala Lys Cys Gly Glu
 65 70 75 80
 Asn Gly Ser Ala Glu Arg Thr Asp Leu Gly Gly Asn Lys Tyr Asn Gln
 85 90 95
 Glu Arg Ile Gln Ile Glu Tyr Val Glu Val Leu Phe Ala Asp Phe Phe
 100 105 110
 Arg Glu Val Phe Ala Ile Cys Gly Ser Cys Asp Ala Leu Gly Asn Trp
 115 120 125
 Asn Pro Gln Asn Ala Val Ala Leu Leu Pro Glu Asn Asp Thr Gly Glu
 130 135 140
 Ser Met Leu Trp Lys Ala Thr Ile Val Leu Ser Arg Gly Val Ser Val
 145 150 155 160
 Gln Tyr Arg Tyr Phe Lys Gly Tyr Phe Leu Glu Pro Lys Glu Asn Ile
 165 170 175
 His His Arg Gly Asp Phe Leu Val Thr Phe Pro Ser Ser Ser Arg Ser
 180 185 190
 Ser Phe Val Gln Thr Gly Gln Phe Ser Gly Arg Asp Ile Asp Lys Asp
 195 200 205
 Pro Lys Leu Ser Pro Val Gly Arg Gly Trp Gly Phe Glu Trp Ala Ile
 210 215 220
 Glu Leu Cys Met Ala Val Lys Glu Asp Val Arg Gln Glu Val Gly Ser
 225 230 235 240
 His Ile Gly Leu Leu Pro Asp Val Ala Met Ala Phe Val Asn Cys Arg
 245 250 255
 Gly Thr Asp Gly Ser Val Ala Val Arg Met Thr Arg Gly His Ser His
 260 265 270
 Cys His Leu Gly Phe Ala Tyr Cys Ala Ser Gly Phe Ser Leu Glu Pro
 275 280 285
 Cys Val Glu Asn Asp Cys Gly Ala Ser Ser Ala Glu Val Gln Gln Gly
 290 295 300
 Phe Val Phe Ile Thr Ser Ala Ser Ser Ser Ser Tyr Cys Thr Glu
 305 310 315 320
 Ala Lys Arg Val Lys Leu Thr Leu Glu Gly Leu Glu Glu Asp Asp Asp
 325 330 335
 Asp Arg Val Ser Pro Thr Val Leu His Lys Met Ser Asn Ser Leu Glu
 340 345 350
 Ile Ser Leu Ile Ser Asp Asn Glu Phe Lys Cys Arg His Ser Gln Pro
 355 360 365
 Glu Cys Gly Tyr Gly Leu Gln Pro Asp Arg Trp Thr Glu Tyr Ser Ile
 370 375 380
 Gln Thr Met Glu Pro Asp Asn Leu Glu Leu Ile Phe Asp Phe Phe Glu
 385 390 395 400
 Glu Asp Leu Ser Glu His Val Val Gln Gly Asp Ala Leu Pro Gly His
 405 410 415
 Val Gly Thr Ala Cys Leu Leu Ser Ser Thr Ile Ala Glu Ser Gly Lys
 420 425 430
 Ser Ala Gly Ile Leu Thr Leu Pro Ile Met Ser Arg Asn Ser Arg Lys
 435 440 445
 Thr Ile Gly Lys Val Arg Val Asp Tyr Ile Ile Ile Lys Pro Leu Pro

```

      450              455              460
Gly Tyr Ser Cys Asp Met Lys Ser Ser Phe Ser Lys Tyr Trp Lys Pro
465              470              475              480
Arg Ile Pro Leu Asp Val Gly His Arg Gly Ala Gly Asn Ser Thr Thr
      485              490              495
Thr Ala Gln Leu Ala Lys Val Gln Glu Asn Thr Ile Ala Ser Leu Arg
      500              505              510
Asn Ala Ala Ser His Gly Ala Ala Phe Val Glu Phe Asp Val His Leu
      515              520              525
Ser Lys Asp Phe Val Pro Val Val Tyr His Asp Leu Thr Cys Cys Leu
      530              535              540
Thr Met Lys Lys Lys Phe Asp Ala Asp Pro Val Glu Leu Phe Glu Ile
545              550              555              560
Pro Val Lys Glu Leu Thr Phe Asp Gln Leu Gln Leu Leu Lys Leu Thr
      565              570              575
His Val Thr Ala Leu Lys Ser Lys Asp Arg Lys Glu Ser Val Val Gln
      580              585              590
Glu Glu Asn Ser Phe Ser Glu Asn Gln Pro Phe Pro Ser Leu Lys Met
      595              600              605
Asp Gly Met Trp Asp Gly Asn Leu Ser Thr Tyr Phe Asp Met Asn Leu
      610              615              620
Phe Leu Asp Ile Ile Leu Lys Thr Val Leu Glu Asn Ser Gly Lys Arg
625              630              635              640
Arg Ile Val Phe Ser Ser Phe Asp Ala Asp Ile Cys Thr Met Val Arg
      645              650              655
Gln Lys Gln Asn Lys Tyr Pro Ile Leu Phe Leu Thr Gln Gly Lys Ser
      660              665              670
Glu Ile Tyr Pro Glu Leu Met Asp Leu Arg Ser Arg Thr Thr Pro Ile
      675              680              685
Ala Met Ser Phe Ala Gln Phe Glu Asn Leu Leu Gly Ile Asn Val His
      690              695              700
Thr Glu Asp Leu Leu Arg Asn Pro Ser Tyr Ile Gln Glu Ala Lys Ala
705              710              715              720
Lys Gly Leu Val Ile Phe Cys Trp Gly Asp Asp Thr Asn Asp Pro Glu
      725              730              735
Asn Arg Arg Lys Leu Lys Glu Leu Gly Val Asn Gly Leu Ile Tyr Asp
      740              745              750
Arg Ile Tyr Asp Trp Met Pro Glu Gln Pro Asn Ile Phe Gln Val Glu
      755              760              765
Gln Leu Glu Arg Leu Lys Gln Glu Leu Pro Glu Leu Lys Ser Cys Leu
      770              775              780
Cys Pro Thr Val Ser Arg Phe Val Pro Ser Ser Leu Cys Gly Glu Ser
785              790              795              800
Asp Ile His Val Asp Ala Asn Gly Ile Asp Asn Val Glu Asn Ala
      805              810              815

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<210> 261
 <211> 1083
 <212> PRT
 <213> Homo sapiens

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      <400> 261
Met Glu Pro Ile Glu Gly Lys Arg Ser Ser Cys His Lys Thr Gly Glu
  1              5              10              15
Ala Thr Ala Val Val His Cys Pro Pro Gly Trp Asn Ile Thr Met Gly
      20              25              30
Val Glu Ala Ser Cys Ala Phe Val Gly Arg Ala Gly Ser Gln Asp Thr
      35              40              45
Val Arg Thr Gly Arg Ala Leu Lys Ala Leu Thr Gln Leu Arg Ala Ala
      50              55              60
Gln Gly Arg Gly Ser Gln Gly Ala Ala Ala Ala Glu Thr Gly Leu Gly

```

65					70					75				80	
Gly	Arg	Arg	Leu	Arg	Arg	Ala	Pro	Gly	Gly	Gly	Pro	Cys	Val	Gly	Pro
				85					90					95	
Arg	Ala	Ala	Ala	Ala	Thr	Thr	Leu	Ser	Gly	Pro	Arg	Gly	Thr	Ala	Gln
			100					105					110		
Gly	His	Gly	Gly	Gly	Gly	Arg	Ser	Ser	Gly	Lys	Gly	Asp	Gln	Arg	Ala
	115					120						125			
His	Glu	Leu	Ala	Ala	Trp	Ile	Pro	Arg	Ala	Thr	Arg	Ala	Arg	His	Thr
	130					135					140				
Gly	Ala	Ala	Gly	Ala	Glu	Pro	Tyr	Tyr	Arg	Ala	Trp	Gly	Ser	Gly	Glu
145					150					155					160
Gln	Gly	Arg	Gly	Val	Cys	Arg	Gly	Leu	Leu	Arg	Leu	Pro	Ala	Gly	Pro
			165					170						175	
Pro	Thr	Pro	Gly	Arg	Ala	Arg	Ala	Leu	Ala	Glu	Arg	Leu	Ser	Pro	Pro
			180					185					190		
Arg	Ala	Ala	Pro	Arg	Gln	Asp	Ser	Trp	Pro	Leu	Arg	Gly	Phe	Leu	Pro
	195					200						205			
Pro	Pro	Gln	Pro	Leu	Asn	Pro	Thr	Ser	Ala	Ser	Pro	His	Pro	Arg	Leu
	210					215					220				
Phe	Ser	Leu	Leu	Gly	Ala	Arg	Pro	Ile	Ser	Pro	Trp	Thr	Met	Ala	Ala
225					230					235					240
Thr	Ile	Gln	Ala	Met	Glu	Arg	Lys	Ile	Glu	Ser	Gln	Ala	Ala	His	Leu
			245						250					255	
Leu	Ser	Leu	Glu	Gly	Gln	Thr	Gly	Met	Ala	Glu	Lys	Lys	Leu	Ala	Asp
		260						265					270		
Cys	Glu	Lys	Thr	Ala	Val	Glu	Phe	Gly	Asn	Gln	Leu	Glu	Gly	Lys	Trp
	275						280					285			
Ala	Val	Leu	Gly	Thr	Leu	Leu	Gln	Glu	Tyr	Gly	Leu	Leu	Gln	Arg	Arg
	290					295					300				
Leu	Glu	Asn	Val	Glu	Asn	Leu	Leu	His	Asn	Arg	Asn	Phe	Trp	Ile	Leu
305					310					315					320
Arg	Leu	Pro	Pro	Gly	Ser	Lys	Gly	Glu	Ser	Pro	Lys	Val	Ala	Leu	Gly
			325						330					335	
Arg	Pro	Gly	Val	Gly	Glu	Ala	Ala	Ala	Lys	Pro	Val	Ser	Val	Trp	Phe
		340						345					350		
Ser	Glu	Gln	Val	Trp	Gly	Lys	Leu	Glu	Asp	Trp	Gln	Lys	Glu	Leu	Cys
	355					360						365			
Lys	His	Val	Met	Arg	Gly	Asn	Cys	Glu	Met	Leu	Val	Ser	Leu	Asp	Tyr
	370					375					380				
Ala	Ile	Ser	Lys	Ser	Glu	Val	Leu	Ser	Gln	Ile	Glu	Gln	Gly	Lys	Glu
385					390					395					400
Pro	Cys	Asn	Trp	Arg	Arg	Pro	Gly	Pro	Lys	Ile	Pro	Asp	Val	Pro	Val
			405						410					415	
Asp	Pro	Ser	Pro	Ala	Pro	Val	Pro	Leu	Pro	Leu	Phe	Cys	Ser	Leu	Tyr
		420						425					430		
Pro	Pro	Gly	Glu	Ile	His	Gln	Cys	Ser	Val	Pro	Ala	Ala	Lys	Gln	Leu
	435					440						445			
His	Val	Val	Gln	Arg	Thr	Ser	Pro	Val	Thr	Ala	Lys	Leu	Ser	Thr	Leu
	450					455					460				
Gln	Pro	Lys	Pro	His	Phe	His	Leu	Val	Leu	His	Pro	Thr	Pro	Cys	Gln
465					470					475					480
Leu	Leu	Lys	Gly	Asn	Thr	Val	Asn	Pro	Thr	Leu	Thr	Ser	Thr	Pro	Thr
			485						490					495	
Ala	Thr	Ala	Cys	Phe	Ser	Ala	Pro	Leu	Arg	Gly	Arg	Ala	Pro	Trp	Ile
		500						505					510		
Tyr	Thr	Met	Glu	Gly	Asn	Arg	Leu	Asn	Gln	Cys	Phe	Gln	Thr	Gly	Cys
	515						520					525			
Trp	Arg	Ala	Pro	Gly	His	Ile	Gln	Ala	Gly	Glu	Glu	Ala	Pro	Gly	Ser
	530					535					540				
Arg	Val	Val	Phe	Thr	Arg	Ile	Thr	Gly	Ser	Gly	Glu	Cys	Arg	Arg	Gly
545					550					555					560
Pro	Glu	Lys	Ser	Cys	Gly	Phe	Gly	His	Ser	Arg	Glu	Ala	Leu	Gly	Glu
			565					570						575	
Glu	Trp	Met	Ile	Arg	Lys	Val	Lys	Val	Glu	Asp	Glu	Asp	Gln	Glu	Ala

[illegible]

<210> 262
 <211> 738
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> misc_feature
 <222> (1)...(738)
 <223> Xaa = X or * as defined in Table 6

<400> 262
 Ile Thr Met Gly Ser Ser Gly Leu Gly Lys Ala Ala Thr Leu Asp Glu
 1 5 10 15
 Leu Leu Cys Thr Cys Ile Glu Met Phe Asp Asp Asn Gly Glu Leu Asp
 20 25 30
 Asn Ser Tyr Leu Pro Arg Ile Val Leu Leu Met His Arg Trp Tyr Leu
 35 40 45
 Ser Ser Thr Glu Leu Ala Glu Lys Leu Leu Cys Met Tyr Arg Asn Ala
 50 55 60
 Thr Gly Glu Ser Cys Asn Glu Phe Arg Leu Lys Ile Cys Tyr Phe Met
 65 70 75 80
 Arg Tyr Trp Ile Leu Lys Phe Pro Ala Glu Phe Asn Leu Asp Leu Gly
 85 90 95
 Leu Ile Arg Met Thr Glu Glu Phe Arg Glu Val Ala Ser Gln Leu Gly
 100 105 110
 Tyr Glu Lys His Val Ser Leu Ile Asp Ile Ser Ser Ile Pro Ser Tyr
 115 120 125
 Asp Trp Met Arg Arg Val Thr Gln Arg Lys Lys Val Ser Lys Lys Gly
 130 135 140
 Lys Ala Cys Leu Leu Phe Asp His Leu Glu Pro Ile Glu Leu Ala Glu
 145 150 155 160
 His Leu Thr Phe Leu Glu His Lys Ser Phe Arg Arg Ile Ser Phe Thr
 165 170 175
 Asp Tyr Gln Ser Tyr Val Ile His Gly Cys Leu Glu Asn Asn Pro Thr
 180 185 190
 Leu Glu Arg Ser Ile Ala Leu Phe Asn Gly Ile Ser Lys Trp Val Gln
 195 200 205
 Leu Met Val Leu Ser Lys Pro Thr Pro Gln Gln Arg Ala Glu Val Ile
 210 215 220
 Thr Lys Phe Ile Asn Val Ala Lys Lys Leu Leu Gln Leu Lys Asn Phe
 225 230 235 240
 Asn Asn Leu Ile Ala Ile Val Gly Ala Leu Ser His Arg Ser Ile Ser
 245 250 255
 Gly Phe Lys Gly Thr His Ser His Leu Ser Ser Glu Val Thr Lys Asn
 260 265 270
 Trp Asn Val Lys Xaa Gln Lys Trp Val Ser Ser Asn Gly Asn Tyr Cys
 275 280 285
 Asn Tyr Arg Lys Pro Phe Ala Asp Cys Asp Gly Phe Lys Ile Pro Ile
 290 295 300
 Leu Gly Val His Leu Lys Asp Leu Ile Ala Val His Val Ile Phe Pro
 305 310 315 320
 Asp Trp Thr Glu Glu Asn Lys Val Asn Ile Val Lys Met His Gln Leu
 325 330 335
 Ser Val Thr Leu Ser Glu Leu Val Ser Leu Gln Asn Ala Ser His His
 340 345 350
 Leu Glu Pro Asn Met Asp Leu Ile Asn Leu Leu Thr Leu Ser Leu Asp
 355 360 365
 Leu Tyr His Thr Glu Asp Asp Ile Tyr Lys Leu Ser Leu Val Leu Glu
 370 375 380
 Pro Arg Asn Ser Lys Ser Gln Pro Thr Ser Pro Thr Thr Pro Asn Lys
 385 390 395 400

```

Pro Val Val Pro Leu Glu Trp Ala Leu Gly Val Met Pro Lys Pro Asp
      405      410      415
Pro Thr Val Ile Asn Lys His Ile Arg Lys Leu Val Glu Ser Val Phe
      420      425      430
Arg Asn Tyr Asp His Asp His Asp Gly Tyr Ile Ser Gln Glu Asp Phe
      435      440      445
Glu Ser Ile Ala Ala Asn Phe Pro Phe Leu Asp Ser Phe Cys Val Leu
      450      455      460
Asp Lys Asp Gln Asp Gly Leu Ile Ser Lys Asp Glu Met Met Ala Tyr
      465      470      475      480
Phe Leu Arg Ala Lys Ser Gln Leu His Cys Gln Ile Gly Ala Pro Gly
      485      490      495
Phe Ile His Asn Phe Gln Glu Met Thr Tyr Leu Lys Pro Thr Phe Cys
      500      505      510
Glu His Cys Ala Gly Phe Ile Leu Gly Ile Ile Lys Gln Gly Tyr Lys
      515      520      525
Cys Lys Asp Cys Gly Ala Asn Cys His Lys Gln Cys Lys Asp Leu Leu
      530      535      540
Val Leu Ala Cys Arg Arg Phe Ala Arg Ala Pro Ser Leu Ser Ser Gly
      545      550      555      560
His Gly Ser Leu Pro Gly Ser Pro Ser Leu Pro Pro Ala Gln Asp Xaa
      565      570      575
Val Phe Lys Phe Pro Gly Val Thr Ala Asp Asn Ser Asp Leu Asp Ser
      580      585      590
Arg Ala Ile Thr Leu Val Thr Gly Ser Ser Arg Lys Thr Ser Val Arg
      595      600      605
Leu Gln Arg Ala Thr Thr Ser Gln Ala Thr Gln Thr Glu Pro Val Trp
      610      615      620
Ser Glu Ala Gly Trp Gly Asp Ser Gly Ser His Thr Leu Pro Tyr Asn
      625      630      635      640
Arg Tyr Ser Gly Ser Leu His Lys Pro Ala Lys Arg His Lys Gly Phe
      645      650      655
Ala Ile Trp Glu Lys Xaa Lys Ser Pro Gly Trp His Ala Gly Gly Asp
      660      665      670
Val Xaa Asn Pro Gly Thr Glu Phe Glu Leu Ala Pro Asp Glu Gly Glu
      675      680      685
Lys Thr Thr Gln Asp Gly Glu Asp Gly Leu Thr Ser Arg Leu Ala Glu
      690      695      700
Asn Leu Lys Ala Asn Asn Gly Trp Leu Leu Gly Gly Gly Lys Asn Lys
      705      710      715      720
Lys Leu Leu Arg Lys Ala Leu Ala Ser Gln Glu Val Ile Leu Glu Arg
      725      730      735
Thr Pro

```

<210> 263

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (80)

<223> Xaa = X or * as defined in Table 6

<400> 263

```

Arg Pro Lys Met Gly Arg Arg Ser Lys His Lys Pro Pro Ala Ser Phe
1      5      10      15
Gln Val Ser Ser Leu Ser Asn Pro Gly Phe Phe Phe Phe Ile Xaa His
      20      25      30
Cys Phe Phe Xaa Leu Tyr Phe Ser Tyr Lys Arg Asn Val Ser Leu Xaa

```


		35						40					45						
Lys	Ile	Thr	His	Tyr	Arg	Lys	Ile	Leu	Arg	Arg	Lys	Thr	Phe	Thr	Ser				
	50						55					60							
Glu	Thr	Lys	Phe	Phe	Pro	Met	Lys	Thr	Glu	Pro	Lys	Arg	Val	Ser	Gly				
	65					70				75					80				

<210> 264
 <211> 644
 <212> PRT
 <213> Homo sapiens

<400> 264

Met	Pro	Ala	Pro	Arg	Ala	Arg	Glu	Gln	Pro	Arg	Val	Pro	Gly	Glu	Arg				
1				5					10					15					
Gln	Pro	Leu	Leu	Pro	Arg	Gly	Ala	Arg	Gly	Pro	Arg	Arg	Trp	Arg	Arg				
			20					25					30						
Ala	Ala	Gly	Ala	Ala	Val	Leu	Leu	Val	Glu	Met	Leu	Glu	Arg	Ala	Ala				
		35					40					45							
Phe	Phe	Gly	Val	Thr	Ala	Asn	Leu	Val	Leu	Tyr	Leu	Asn	Ser	Thr	Asn				
	50					55					60								
Phe	Asn	Trp	Thr	Gly	Glu	Gln	Ala	Thr	Arg	Ala	Ala	Leu	Val	Phe	Leu				
	65				70				75					80					
Gly	Ala	Ser	Tyr	Leu	Leu	Ala	Pro	Val	Gly	Gly	Trp	Leu	Ala	Asp	Val				
				85					90					95					
Tyr	Leu	Gly	Arg	Tyr	Arg	Ala	Val	Ala	Leu	Ser	Leu	Leu	Leu	Tyr	Leu				
		100						105					110						
Ala	Ala	Ser	Gly	Leu	Leu	Pro	Ala	Thr	Ala	Phe	Pro	Asp	Gly	Arg	Ser				
		115				120						125							
Ser	Phe	Cys	Gly	Glu	Met	Pro	Ala	Ser	Pro	Leu	Gly	Pro	Ala	Cys	Pro				
	130					135					140								
Ser	Ala	Gly	Cys	Pro	Arg	Ser	Ser	Pro	Ser	Pro	Tyr	Cys	Ala	Pro	Val				
	145				150					155				160					
Leu	Tyr	Ala	Gly	Leu	Leu	Leu	Leu	Gly	Leu	Ala	Ala	Ser	Ser	Val	Arg				
				165				170						175					
Ser	Asn	Leu	Thr	Ser	Phe	Gly	Ala	Asp	Gln	Val	Met	Asp	Leu	Gly	Arg				
		180					185						190						
Asp	Ala	Thr	Arg	Arg	Phe	Phe	Asn	Trp	Phe	Tyr	Trp	Ser	Ile	Asn	Leu				
	195					200						205							
Gly	Ala	Val	Leu	Ser	Leu	Leu	Val	Val	Ala	Phe	Ile	Gln	Gln	Asn	Ile				
	210					215					220								
Ser	Phe	Leu	Leu	Gly	Tyr	Ser	Ile	Pro	Val	Gly	Cys	Val	Gly	Leu	Ala				
	225				230					235				240					
Phe	Phe	Ile	Phe	Leu	Phe	Ala	Thr	Pro	Val	Phe	Ile	Thr	Lys	Pro	Pro				
			245					250					255						
Met	Gly	Ser	Gln	Val	Ser	Ser	Met	Leu	Lys	Leu	Ala	Leu	Gln	Asn	Cys				
		260					265						270						
Cys	Pro	Gln	Leu	Trp	Gln	Arg	His	Ser	Ala	Arg	Ser	Lys	Leu	Ser	Gln				
	275					280						285							
Gly	Gln	Gln	Gly	Asn	Asn	Gly	Ser	Glu	Ser	Lys	Leu	His	Leu	Leu	Val				
	290				295						300								
Ala	Lys	Trp	Gln	His	Thr	Leu	Gly	Arg	Val	Glu	Leu	Thr	Val	Ala	Val				
	305				310					315				320					
Phe	Gly	Asp	Asp	Tyr	Thr	Asn	Ile	Val	Pro	Phe	Gly	Ile	Ser	Lys	Asp				
			325					330					335						
Ser	Ala	Arg	Leu	Leu	Asp	Lys	Lys	Arg	Asp	Arg	Gln	Cys	Ala	Arg	Val				
		340					345					350							
Leu	Ala	Asp	Glu	Arg	Ser	Pro	Gln	Pro	Gly	Ala	Ser	Pro	Gln	Glu	Asp				
	355					360						365							
Ile	Ala	Asn	Phe	Gln	Val	Leu	Val	Lys	Ile	Leu	Pro	Val	Met	Val	Thr				

```

      370              375              380
Leu Val' Pro Tyr Trp Met Val Tyr Phe Gln Met Gln Ser Thr Tyr Val
385              390              395              400
Leu Gln Gly Leu His Leu His Ile Pro Asn Ile Phe Pro Ala Asn Pro
      405              410              415
Ala Asn Ile Ser Val Ala Leu Arg Ala Gln Gly Ser Ser Tyr Thr Ile
      420              425              430
Pro Glu Ala Trp Leu Leu Leu Ala Asn Val Val Val Val Leu Ile Leu
      435              440              445
Val Pro Leu Lys Asp Arg Leu Ile Asp Pro Leu Leu Leu Arg Cys Lys
      450              455              460
Leu Leu Pro Ser Ala Leu Gln Lys Met Ala Leu Gly Met Phe Phe Gly
465              470              475              480
Phe Thr Ser Val Ile Val Ala Gly Val Leu Glu Met Glu Arg Leu His
      485              490              495
Tyr Ile His His Asn Glu Thr Val Ser Gln Gln Ile Gly Glu Val Leu
      500              505              510
Tyr Asn Ala Ala Pro Leu Ser Ile Trp Trp Gln Ile Pro Gln Tyr Leu
      515              520              525
Leu Ile Gly Ile Ser Glu Ile Phe Ala Ser Ile Pro Gly Leu Glu Phe
      530              535              540
Ala Tyr Ser Glu Ala Pro Arg Ser Met Gln Gly Ala Ile Met Gly Ile
545              550              555              560
Phe Phe Cys Leu Ser Gly Val Gly Ser Leu Leu Gly Ser Ser Leu Val
      565              570              575
Gly Thr Ala Val Pro Leu Pro Gly Gly Trp Leu His Cys Pro Lys Asp
      580              585              590
Phe Gly Asn Ile Asn Asn Cys Arg Met Asp Leu Tyr Phe Phe Leu Leu
      595              600              605
Ala Gly Ile Gln Ala Val Thr Ala Leu Leu Phe Val Trp Ile Ala Gly
      610              615              620
Arg Tyr Glu Arg Ala Ser Gln Gly Pro Ala Ser His Ser Arg Phe Ser
625              630              635              640
Arg Asp Arg Gly

```

```

<210> 265
<211> 99
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(99)
<223> Xaa = X or * as defined in Table 6

```

```

      <400> 265
Xaa Ala Cys Ser Gly Val Pro Gly Thr Lys Cys Ser Pro Pro Ser Gly
  1              5              10              15
Ser Gly Tyr Pro Asn Pro Tyr Ser Lys His Val Leu Thr Glu Asp Ile
      20              25              30
Val His Arg Glu Val Thr Pro Asp Gln Lys Leu Leu Ser Arg Ala Thr
      35              40              45
Leu Thr Lys Thr Asn Arg Asn Ala His Ala Gly Pro Glu Arg Leu Phe
      50              55              60
Pro Ala Asn Val Ala His Ser Val Tyr Val Leu Glu Asp Ser Ile Val
      65              70              75              80
Asp Pro Gln Asn Gln Thr Leu Thr Thr Phe Asn Trp Asn Ile Asn Pro
      85              90              95
Arg Pro Gly

```

<210> 266
 <211> 840
 <212> PRT
 <213> Homo sapiens

<400> 266
 Ser Ser Leu Thr Ser Ser Met Glu Asp Pro Ala Ala Pro Gly Thr Gly
 1 5 10 15
 Gly Pro Pro Ala Asn Gly Asn Gly Asn Gly Gly Gly Lys Gly Lys Gln
 20 25 30
 Ala Ala Pro Lys Gly Arg Glu Ala Phe Arg Ser Gln Arg Arg Glu Ser
 35 40 45
 Glu Gly Ser Val Asp Cys Pro Thr Leu Glu Phe Glu Tyr Gly Asp Ala
 50 55 60
 Asp Gly His Ala Ala Glu Leu Ser Glu Leu Tyr Ser Tyr Thr Glu Asn
 65 70 75 80
 Leu Glu Phe Thr Asn Asn Arg Arg Cys Phe Glu Glu Asp Phe Lys Thr
 85 90 95
 Gln Val Gln Gly Lys Glu Trp Leu Glu Leu Glu Glu Asp Ala Gln Lys
 100 105 110
 Ala Tyr Ile Met Gly Leu Leu Asp Arg Leu Glu Val Val Ser Arg Glu
 115 120 125
 Arg Arg Leu Lys Ala Ala Arg Ala Val Leu Tyr Leu Ala Gln Gly Thr
 130 135 140
 Phe Gly Glu Cys Asp Ser Glu Val Asp Val Leu His Trp Ser Arg Tyr
 145 150 155 160
 Asn Cys Phe Leu Leu Tyr Gln Met Gly Thr Phe Ser Thr Phe Leu Glu
 165 170 175
 Leu Leu His Met Glu Ile Asp Asn Ser Gln Ala Cys Ser Ser Ala Leu
 180 185 190
 Arg Lys Pro Ala Val Ser Ile Ala Asp Ser Thr Glu Leu Arg Val Leu
 195 200 205
 Leu Ser Val Met Tyr Leu Met Val Glu Asn Ile Arg Leu Glu Arg Glu
 210 215 220
 Thr Asp Pro Cys Gly Trp Arg Thr Ala Arg Glu Thr Phe Arg Thr Glu
 225 230 235 240
 Leu Ser Phe Ser Met His Asn Glu Glu Pro Phe Ala Leu Leu Leu Phe
 245 250 255
 Ser Met Val Thr Lys Phe Cys Ser Gly Leu Ala Pro His Phe Pro Ile
 260 265 270
 Lys Lys Val Leu Leu Leu Leu Trp Lys Val Val Met Phe Thr Leu Gly
 275 280 285
 Gly Phe Glu His Leu Gln Thr Leu Lys Val Gln Lys Arg Ala Glu Leu
 290 295 300
 Gly Leu Pro Pro Leu Ala Glu Asp Ser Ile Gln Val Val Lys Ser Met
 305 310 315 320
 Arg Ala Ala Ser Pro Pro Ser Tyr Thr Leu Asp Leu Gly Glu Ser Gln
 325 330 335
 Leu Ala Pro Pro Pro Ser Lys Leu Arg Gly Arg Arg Gly Ser Arg Arg
 340 345 350
 Gln Leu Leu Thr Lys Gln Asp Ser Leu Asp Ile Tyr Asn Glu Arg Asp
 355 360 365
 Leu Phe Lys Thr Glu Glu Pro Ala Thr Glu Glu Glu Glu Glu Ser Ala
 370 375 380
 Gly Asp Gly Glu Arg Thr Leu Asp Gly Glu Leu Asp Leu Leu Glu Gln
 385 390 395 400
 Asp Pro Leu Val Pro Pro Pro Ser Gln Ala Pro Leu Ser Ala Glu
 405 410 415
 Arg Val Ala Phe Pro Lys Gly Leu Pro Trp Ala Pro Lys Val Arg Gln
 420 425 430

Lys Asp Ile Glu His Phe Leu Glu Met Ser Arg Asn Lys Phe Ile Gly
 435 440 445
 Phe Thr Leu Gly Gln Asp Thr Asp Thr Leu Val Gly Leu Pro Arg Pro
 450 455 460
 Ile His Glu Ser Val Lys Thr Leu Lys Gln His Lys Tyr Ile Ser Ile
 465 470 475 480
 Ala Asp Val Gln Ile Lys Asn Glu Glu Glu Leu Glu Lys Cys Pro Met
 485 490 495
 Ser Leu Gly Glu Glu Val Val Pro Glu Thr Pro Cys Glu Ile Leu Tyr
 500 505 510
 Gln Gly Met Leu Tyr Ser Leu Pro Gln Tyr Met Ile Ala Leu Leu Lys
 515 520 525
 Ile Leu Leu Ala Ala Ala Pro Thr Ser Lys Ala Lys Thr Asp Ser Ile
 530 535 540
 Asn Ile Leu Ala Asp Val Leu Pro Glu Glu Met Pro Ile Thr Val Leu
 545 550 555 560
 Gln Ser Met Lys Leu Gly Ile Asp Val Asn Arg His Lys Glu Ile Ile
 565 570 575
 Val Lys Ser Ile Ser Thr Leu Leu Leu Leu Leu Lys His Phe Lys
 580 585 590
 Leu Asn His Ile Tyr Gln Phe Glu Tyr Val Ser Gln His Leu Val Phe
 595 600 605
 Ala Asn Cys Ile Pro Leu Ile Leu Lys Phe Phe Asn Gln Asn Ile Leu
 610 615 620
 Ser Tyr Ile Thr Ala Lys Asn Ser Ile Ser Val Leu Asp Tyr Pro Cys
 625 630 635 640
 Cys Thr Ile Gln Asp Leu Pro Glu Leu Thr Thr Glu Ser Leu Glu Ala
 645 650 655
 Gly Asp Asn Ser Gln Phe Cys Trp Arg Asn Leu Phe Ser Cys Ile Asn
 660 665 670
 Leu Leu Arg Leu Leu Asn Lys Leu Thr Lys Trp Lys His Ser Arg Thr
 675 680 685
 Met Met Leu Val Val Phe Lys Ser Ala Pro Ile Leu Lys Arg Ala Leu
 690 695 700
 Lys Val Lys Gln Ala Met Leu Gln Leu Tyr Val Leu Lys Leu Leu Lys
 705 710 715 720
 Leu Gln Thr Lys Tyr Leu Gly Arg Gln Trp Arg Lys Ser Asn Met Lys
 725 730 735
 Thr Met Ser Ala Ile Tyr Gln Lys Val Arg His Arg Met Asn Asp Asp
 740 745 750
 Trp Ala Tyr Gly Asn Asp Ile Asp Ala Arg Pro Trp Asp Phe Gln Ala
 755 760 765
 Glu Glu Cys Thr Leu Arg Ala Asn Ile Glu Ala Phe Asn Ser Arg Arg
 770 775 780
 Tyr Asp Arg Pro Gln Asp Ser Glu Phe Ser Pro Val Asp Asn Cys Leu
 785 790 795 800
 Gln Ser Val Leu Gly Gln Arg Leu Asp Leu Pro Glu Asp Phe His Tyr
 805 810 815
 Ser Tyr Glu Leu Trp Leu Glu Arg Glu Val Phe Ser Gln Pro Ile Cys
 820 825 830
 Trp Glu Glu Leu Leu Gln Asn His
 835 840

<210> 267

<211> 308

<212> PRT

<213> Homo sapiens

<400> 267

Pro Ala Trp Asn Ala Arg Pro Arg Gln Val Asp Leu Lys Leu Thr His
 1 5 10 15

Lys Lys Gln Arg Ala Leu Leu Glu Arg Phe Asp Ile Tyr Arg Lys Val
 20 25 30
 Pro Lys Asp Leu Thr Gln Pro Thr Tyr Thr Gly Ala Ile Ile Ser Ile
 35 40 45
 Cys Cys Cys Leu Phe Ile Leu Phe Leu Phe Leu Ser Glu Leu Thr Gly
 50 55 60
 Phe Ile Thr Thr Glu Val Val Asn Glu Leu Tyr Val Asp Asp Pro Asp
 65 70 75 80
 Lys Asp Ser Gly Gly Lys Ile Asp Val Ser Leu Asn Ile Ser Leu Pro
 85 90 95
 Asn Leu His Cys Glu Leu Val Gly Leu Asp Ile Gln Asp Glu Met Gly
 100 105 110
 Arg His Glu Val Gly His Ile Asp Asn Ser Met Lys Ile Pro Leu Asn
 115 120 125
 Asn Gly Ala Gly Cys Arg Phe Glu Gly Gln Phe Ser Ile Asn Lys Val
 130 135 140
 Pro Gly Asn Phe His Val Ser Thr His Ser Ala Thr Ala Gln Pro Gln
 145 150 155 160
 Asn Pro Asp Met Thr His Val Ile His Lys Leu Ser Phe Gly Asp Thr
 165 170 175
 Leu Gln Val Gln Asn Ile His Gly Ala Phe Asn Ala Leu Gly Gly Ala
 180 185 190
 Asp Arg Leu Thr Ser Asn Pro Leu Ala Ser His Asp Tyr Ile Leu Lys
 195 200 205
 Ile Val Pro Thr Val Tyr Glu Asp Lys Ser Gly Lys Gln Arg Tyr Ser
 210 215 220
 Tyr Gln Tyr Thr Val Ala Asn Lys Glu Tyr Val Ala Tyr Ser His Thr
 225 230 235 240
 Gly Arg Ile Ile Pro Ala Ile Trp Phe Arg Tyr Asp Leu Ser Pro Ile
 245 250 255
 Thr Val Lys Tyr Thr Glu Arg Arg Gln Pro Leu Tyr Arg Phe Ile Thr
 260 265 270
 Thr Ile Cys Ala Ile Ile Gly Gly Thr Phe Thr Val Ala Gly Ile Leu
 275 280 285
 Asp Ser Cys Ile Phe Thr Ala Ser Glu Ala Trp Lys Lys Ile Gln Leu
 290 295 300
 Gly Lys Met His
 305

<210> 268
 <211> 162
 <212> PRT
 <213> Homo sapiens

<400> 268
 Met Leu Ile Tyr Ser Ser Lys Thr Leu Glu Leu Arg Glu Thr Ser Val
 1 5 10 15
 Thr Pro Ser Asn Leu Trp Gly Gly Gln Gly Leu Leu Gly Val Ser Ile
 20 25 30
 Arg Phe Cys Ser Phe Asp Gly Ala Asn Glu Asn Val Trp His Val Leu
 35 40 45
 Glu Val Glu Ser Asn Ser Pro Ala Ala Leu Ala Gly Leu Arg Pro His
 50 55 60
 Ser Asp Tyr Ile Ile Gly Ala Asp Thr Val Met Asn Glu Ser Glu Asp
 65 70 75 80
 Leu Phe Ser Leu Ile Glu Thr His Glu Ala Lys Pro Leu Lys Leu Tyr
 85 90 95
 Val Tyr Asn Thr Asp Thr Val Tyr Thr Gly Asn Ser Thr Trp Lys Thr
 100 105 110
 Cys Val Lys Ser Ser Tyr Ser Gly Ala Leu Val Asn Leu Asn Arg Leu
 115 120 125

```

Phe Ser Ser Ala Tyr Thr Arg Ile Pro Cys Phe Gly Ala Leu Arg Ile
  130      135      140
Asn Ser Asp Lys His Phe Val Asn Gly Cys Trp Leu Leu Ser Thr Tyr
 145      150      155      160
Thr Leu

```

```

<210> 269
<211> 280
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(280)
<223> Xaa = X or * as defined in Table 6

```

```

<400> 269
Asn Leu Leu Leu Gly Gly Gly Lys Lys Lys Lys Pro Pro Arg Thr
 1      5      10      15
Arg Gly Pro Phe Pro Gly Leu Ser Gln Pro Gly Leu Leu Trp Leu Phe
      20      25      30
Pro Lys Arg Pro Gly Cys Ser His Leu Pro Ser Thr Pro Ile Lys Glu
      35      40      45
Met Gly Leu Pro Lys Ile His His Arg Val Gly Trp Glu Ser Phe Ser
 50      55      60
Gly Val Phe Leu Glu Val Asp Phe Lys Ile Tyr Lys Lys Lys Met Asn
 65      70      75      80
Glu Phe Phe Ser Val Asp Asp Asn Asn Glu Glu Glu Glu Asp Val Glu
      85      90      95
Met Lys Glu Asp Ser Asp Glu Asn Gly Pro Glu Glu Lys Gln Ser Val
      100      105      110
Glu Glu Met Glu Glu Gln Ser Gln Asp Ala Asp Gly Val Asn Thr Val
      115      120      125
Thr Val Pro Gly Pro Ala Ser Glu Glu Ala Val Glu Asp Cys Lys Asp
      130      135      140
Glu Asp Phe Ala Lys Asp Glu Asn Ile Thr Lys Gly Gly Glu Val Thr
 145      150      155      160
Asp His Ser Val Arg Asp Gln Asp His Pro Asp Gly Gln Glu Asn Asp
      165      170      175
Ser Thr Lys Asn Glu Ile Lys Ile Glu Thr Glu Ser Gln Ser Ser Tyr
      180      185      190
Met Glu Thr Glu Glu Leu Ser Ser Asn Gln Glu Asp Ala Val Ile Val
      195      200      205
Glu Gln Pro Glu Val Ile Pro Leu Thr Glu Asp Gln Glu Glu Lys Glu
      210      215      220
Gly Glu Lys Ala Pro Gly Glu Asp Thr Pro Arg Met Pro Gly Lys Ser
 225      230      235      240
Glu Gly Ser Ser Asp Leu Glu Asn Thr Pro Gly Pro Asp Val Glu Met
      245      250      255
Asn Ser Gln Val Asp Lys Val Asn Asp Pro Thr Glu Ser Gln Pro Ser
      260      265      270
Cys Gln Ala Xaa Arg Ser Arg Gly
      275      280

```

```

<210> 270
<211> 160
<212> PRT
<213> Homo sapiens

```

<220>
 <221> misc_feature
 <222> (1)...(160)
 <223> Xaa = X or * as defined in Table 6

<400> 270
 Glu Arg Arg Glu Arg Ser Pro Asp Gln Ser Ser Gly Arg Ala Ser Arg
 1 5 10 15
 Gly Pro Pro Glu Arg Gln Ser Leu Arg Met Ser Pro Ser Arg Ala Ala
 20 25 30
 Trp Thr Ser Ser Pro Cys Arg Ser Cys Ala Ser Gln Gly Val Cys Ala
 35 40 45
 Trp Pro Leu Asn Leu Arg Arg Ile Ala Ser Thr Ser Trp Cys Xaa Pro
 50 55 60
 Met Ser Ala Gly Ile Gly Pro Met Ala Trp Trp Pro Ser Thr Thr Gly
 65 70 75 80
 Pro Cys Met Met Ser Thr Val Ser Thr Met Ala Lys Pro His Arg Glu
 85 90 95
 Cys Pro Gly Cys Phe Val Pro Phe Ala Val Cys Val Val Ser Arg Phe
 100 105 110
 Pro Tyr Tyr Asn Ser Leu Lys Asp Cys Leu Ser Trp His Tyr Arg Arg
 115 120 125
 Pro Gly Ala Thr Leu Leu Ser Pro Ser Ser Leu Val Thr Leu Leu Leu
 130 135 140
 Val Lys Gly Pro Gly Ala Ala Ala Asp Ala Gly Glu Ile Pro Val
 145 150 155 160

<210> 271
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 271
 Ala Ser Ala Pro Val Gly Cys Leu Thr Arg Ala Val Cys Gly Arg Pro
 1 5 10 15
 Pro Trp Arg Thr Asn Thr Val Val Glu Pro Arg Glu Gly Thr Arg Ile
 20 25 30
 Leu Glu Phe Gly His Leu Lys Leu Ala His Val Pro Pro Leu Glu Phe
 35 40 45
 Leu Val Asn Gln His Gln Pro Glu Asp His Val Leu Ile Lys Arg Trp
 50 55 60
 Lys Glu Glu Lys Leu Glu Pro Ala Trp Glu Gly Pro Tyr Pro Val Leu
 65 70 75 80
 Leu Thr Thr Lys Thr Ala Val Arg Thr Asp Lys Lys Lys Lys Lys Lys
 85 90 95
 Lys Lys Arg Trp Thr His His Thr Gln Val Lys Lys Val Pro Pro Pro
 100 105 110
 Pro Glu Ser Trp Ala Ile Val Pro Gly Glu Asn Pro Thr Lys Leu Lys
 115 120 125
 Leu Arg Lys Met
 130

<210> 272
 <211> 1262
 <212> PRT

<213> Homo sapiens

<400> 272

```

Met Arg Arg Gly Gly Trp Arg Lys Arg Ala Glu Asn Asp Gly Trp Glu
 1          5          10          15
Thr Trp Gly Gly Tyr Met Ala Ala Lys Val Gln Lys Leu Glu Glu Gln
          20          25          30
Phe Arg Ser Asp Ala Ala Met Gln Lys Asp Gly Thr Ser Ser Thr Ile
          35          40          45
Phe Ser Gly Val Ala Ile Tyr Val Asn Gly Tyr Thr Asp Pro Ser Ala
          50          55          60
Glu Glu Leu Arg Lys Leu Met Met Leu His Gly Gly Gln Tyr His Val
          65          70          75          80
Tyr Tyr Ser Arg Ser Lys Thr Thr His Ile Ile Ala Thr Asn Leu Pro
          85          90          95
Asn Ala Lys Ile Lys Glu Leu Lys Gly Glu Lys Val Ile Arg Pro Glu
          100          105          110
Trp Ile Val Glu Ser Ile Lys Ala Gly Arg Leu Leu Ser Tyr Ile Pro
          115          120          125
Tyr Gln Leu Tyr Thr Lys Gln Ser Ser Val Gln Lys Gly Leu Ser Phe
          130          135          140
Asn Pro Val Cys Arg Pro Glu Asp Pro Leu Pro Gly Pro Ser Asn Ile
          145          150          155          160
Ala Lys Gln Leu Asn Asn Arg Val Asn His Ile Val Lys Lys Ile Glu
          165          170          175
Thr Glu Asn Glu Val Lys Val Asn Gly Met Asn Ser Trp Asn Glu Glu
          180          185          190
Asp Glu Asn Asn Asp Phe Ser Phe Val Asp Leu Glu Gln Thr Ser Pro
          195          200          205
Gly Arg Lys Gln Asn Gly Ile Pro His Pro Arg Gly Ser Thr Ala Ile
          210          215          220
Phe Asn Gly His Thr Pro Ser Ser Asn Gly Ala Leu Lys Thr Gln Asp
          225          230          235          240
Cys Leu Val Pro Met Val Asn Ser Val Ala Ser Arg Leu Ser Pro Ala
          245          250          255
Phe Ser Gln Glu Glu Asp Lys Ala Glu Lys Ser Ser Thr Asp Phe Arg
          260          265          270
Asp Cys Thr Leu Gln Gln Leu Gln Gln Ser Thr Arg Asn Thr Asp Ala
          275          280          285
Leu Arg Asn Pro His Arg Thr Asn Ser Phe Ser Leu Ser Pro Leu His
          290          295          300
Ser Asn Thr Lys Ile Asn Gly Ala His His Ser Thr Val Gln Gly Pro
          305          310          315          320
Ser Ser Thr Lys Ser Thr Ser Ser Val Ser Thr Phe Ser Lys Ala Ala
          325          330          335
Pro Ser Val Pro Ser Lys Pro Ser Asp Cys Asn Phe Ile Ser Asn Phe
          340          345          350
Tyr Ser His Ser Arg Leu His His Ile Ser Met Trp Lys Cys Glu Leu
          355          360          365
Thr Glu Phe Val Asn Thr Leu Gln Arg Gln Ser Asn Gly Ile Phe Pro
          370          375          380
Gly Arg Glu Lys Leu Lys Lys Met Lys Thr Gly Arg Ser Ala Leu Val
          385          390          395          400
Val Thr Asp Thr Gly Asp Met Ser Val Leu Asn Ser Pro Arg His Gln
          405          410          415
Ser Cys Ile Met His Val Asp Met Asp Cys Phe Phe Val Ser Val Gly
          420          425          430
Ile Arg Asn Arg Pro Asp Leu Lys Gly Lys Pro Val Ala Val Thr Ser
          435          440          445
Asn Arg Gly Thr Gly Arg Ala Pro Leu Arg Pro Gly Ala Asn Pro Gln
          450          455          460
Leu Glu Trp Gln Tyr Tyr Gln Asn Lys Ile Leu Lys Gly Lys Ala Ala
          465          470          475          480

```


Asp Ile Pro Asp Ser Ser Leu Trp Glu Asn Pro Asp Ser Ala Gln Ala
 485 490 495
 Asn Gly Ile Asp Ser Val Leu Ser Arg Ala Glu Ile Ala Ser Cys Ser
 500 505 510
 Tyr Glu Ala Arg Gln Leu Gly Ile Lys Asn Gly Met Phe Phe Gly His
 515 520 525
 Ala Lys Gln Leu Cys Pro Asn Leu Gln Ala Val Pro Tyr Asp Phe His
 530 535 540
 Ala Tyr Lys Glu Val Ala Gln Thr Leu Tyr Glu Thr Leu Ala Ser Tyr
 545 550 555 560
 Thr His Asn Ile Glu Ala Val Ser Cys Asp Glu Ala Leu Val Asp Ile
 565 570 575
 Thr Glu Ile Leu Ala Glu Thr Lys Leu Thr Pro Asp Glu Phe Ala Asn
 580 585 590
 Ala Val Arg Met Glu Ile Lys Asp Gln Thr Lys Cys Ala Ala Ser Val
 595 600 605
 Gly Ile Gly Ser Asn Ile Leu Leu Ala Arg Met Ala Thr Arg Lys Ala
 610 615 620
 Lys Pro Asp Gly Gln Tyr His Leu Lys Pro Glu Glu Val Asp Asp Phe
 625 630 635 640
 Ile Arg Gly Gln Leu Val Thr Asn Leu Pro Gly Val Gly His Ser Met
 645 650 655
 Glu Ser Lys Leu Ala Ser Leu Gly Ile Lys Thr Cys Gly Asp Leu Gln
 660 665 670
 Tyr Met Thr Met Ala Lys Leu Gln Lys Glu Phe Gly Pro Lys Thr Gly
 675 680 685
 Gln Met Leu Tyr Arg Phe Cys Arg Gly Leu Asp Asp Arg Pro Val Arg
 690 695 700
 Thr Glu Lys Glu Arg Lys Ser Val Ser Ala Glu Ile Asn Tyr Gly Ile
 705 710 715 720
 Arg Phe Thr Gln Pro Lys Glu Ala Glu Ala Phe Leu Leu Ser Leu Ser
 725 730 735
 Glu Glu Ile Gln Arg Arg Leu Glu Ala Thr Gly Met Lys Gly Lys Arg
 740 745 750
 Leu Thr Leu Lys Ile Met Val Arg Lys Pro Gly Ala Pro Val Glu Thr
 755 760 765
 Ala Lys Phe Gly Gly His Gly Ile Cys Asp Asn Ile Ala Arg Thr Val
 770 775 780
 Thr Leu Asp Gln Ala Thr Asp Asn Ala Lys Ile Ile Gly Lys Ala Met
 785 790 795 800
 Leu Asn Met Phe His Thr Met Lys Leu Asn Ile Ser Asp Met Arg Gly
 805 810 815
 Val Gly Ile His Val Asn Gln Leu Val Pro Thr Asn Leu Asn Pro Ser
 820 825 830
 Thr Cys Pro Ser Arg Pro Ser Val Gln Ser Ser His Phe Pro Ser Gly
 835 840 845
 Ser Tyr Ser Val Arg Asp Val Phe Gln Val Gln Lys Ala Lys Lys Ser
 850 855 860
 Thr Glu Glu Glu His Lys Glu Val Phe Arg Ala Val Asp Leu Glu
 865 870 875 880
 Ile Ser Ser Ala Ser Arg Thr Cys Thr Phe Leu Pro Pro Phe Pro Ala
 885 890 895
 His Leu Pro Thr Ser Pro Asp Thr Asn Lys Ala Glu Ser Ser Gly Lys
 900 905 910
 Trp Asn Gly Leu His Thr Pro Val Ser Val Gln Ser Arg Leu Asn Leu
 915 920 925
 Ser Ile Glu Val Pro Ser Pro Ser Gln Leu Asp Gln Ser Val Leu Glu
 930 935 940
 Ala Leu Pro Pro Asp Leu Arg Glu Gln Val Glu Gln Val Cys Ala Val
 945 950 955 960
 Gln Gln Ala Glu Ser His Gly Asp Lys Lys Lys Glu Pro Val Asn Gly
 965 970 975
 Cys Asn Thr Gly Ile Leu Pro Gln Pro Val Gly Thr Met Ser Leu Leu
 980 985 990

Gln Ile Pro Glu Pro Gln Glu Ser Asn Ser Asp Ala Gly Ile Asn Leu
 995 1000 1005
 Ile Ala Leu Pro Ala Phe Ser Gln Val Asp Pro Glu Val Phe Ala Ala
 1010 1015 1020
 Leu Ser Ala Glu Leu Gln Arg Glu Leu Lys Ala Ala Tyr Asp Gln Arg
 1025 1030 1035 1040
 Gln Arg Gln Gly Glu Asn Ser Thr His Gln Gln Ser Ala Ser Ala Ser
 1045 1050 1055
 Val Pro Lys Asn Pro Leu Ile His Leu Lys Ala Ala Val Lys Glu Lys
 1060 1065 1070
 Lys Arg Asn Lys Lys Lys Lys Thr Ile Gly Ser Pro Lys Arg Ile Gln
 1075 1080 1085
 Ser Pro Leu Asn Asn Lys Leu Leu Asn Ser Pro Ala Lys Thr Leu Pro
 1090 1095 1100
 Gly Ala Cys Gly Ser Pro Gln Lys Leu Ile Asp Gly Phe Leu Lys His
 1105 1110 1115 1120
 Glu Gly Pro Pro Ala Glu Lys Pro Leu Glu Lys Asn Ser Ser Gly Phe
 1125 1130 1135
 Leu Leu Ser Gly Val Pro Gly Leu Ser Ser Leu Gln Ser Asp Pro Ser
 1140 1145 1150
 Leu Gly Cys Val Arg Pro Pro Pro Pro Asn Leu Ala Gly Ala Val Glu
 1155 1160 1165
 Phe Asn Asp Val Lys Thr Leu Leu Arg Glu Trp Val Thr Thr Ile Ser
 1170 1175 1180
 Asp Pro Met Glu Glu Asp Ile Leu Gln Val Val Lys Tyr Cys Thr Asp
 1185 1190 1195 1200
 Leu Ile Glu Asp Lys Asp Leu Glu Lys Leu Asp Leu Val Ile Lys Tyr
 1205 1210 1215
 Met Lys Arg Leu Met Gln Gln Ser Val Glu Ser Val Trp Asn Met Ala
 1220 1225 1230
 Phe Asp Phe Ile Leu Asp Asn Val Gln Val Val Leu Gln Gln Thr Tyr
 1235 1240 1245
 Gly Ser His Ile Lys Ser Tyr Ile Asn Ile Thr Gln Arg Ala
 1250 1255 1260

<210> 273
 <211> 260
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(260)
 <223> Xaa = X or * as defined in Table 6

<400> 273
 Met Ala Glu Thr Glu Glu Arg Ser Leu Asp Asn Phe Phe Ala Lys Arg
 1 5 10 15
 Asp Lys Lys Lys Lys Lys Glu Arg Ser Asn Arg Ala Ala Ser Ala Ala
 20 25 30
 Gly Ala Ala Gly Ser Ala Gly Gly Ser Ser Gly Ala Ala Gly Ala Ala
 35 40 45
 Gly Gly Gly Ala Gly Ala Gly Thr Arg Pro Gly Asp Gly Gly Thr Ala
 50 55 60
 Ser Ala Gly Ala Ala Gly Pro Gly Ala Ala Thr Lys Ala Val Thr Lys
 65 70 75 80
 Asp Glu Asp Glu Trp Lys Glu Leu Glu Gln Lys Glu Val Asp Tyr Ser
 85 90 95
 Gly Leu Arg Val Gln Ala Met Gln Ile Ser Ser Glu Lys Glu Glu Asp
 100 105 110
 Asp Asn Glu Lys Arg Gln Asp Pro Gly Asp Asn Trp Glu Glu Gly Gly

```

      115      120      125
Gly Gly Gly Gly Gly Met Glu Lys Ser Ser Gly Pro Trp Asn Lys Thr
      130      135      140
Ala Pro Val Gln Ala Pro Pro Ala Pro Val Ile Val Thr Glu Thr Pro
145      150      155      160
Glu Pro Ala Met Thr Ser Gly Val Tyr Arg Pro Pro Gly Ala Arg Leu
      165      170      175
Thr Thr Thr Arg Lys Thr Pro Gln Gly Pro Pro Glu Ile Tyr Gln Xaa
      180      185      190
Tyr His Ser Ser His Pro Leu Ala Val Asn Leu Pro Lys His Val Glu
      195      200      205
Ser Arg Lys Asp Lys Glu Met Glu Lys Ser Phe Glu Val Val Arg His
      210      215      220
Lys Asn Arg Gly Arg Asp Glu Val Ser Lys Asn Gln Ala Leu Lys Leu
225      230      235      240
Gln Leu Asp Asn Gln Tyr Ala Val Leu Glu Asn Gln Lys Ser Ser His
      245      250      255
Ser Gln Tyr Asn
      260

```

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<210> 274
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(122)
<223> Xaa = X or * as defined in Table 6

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```

      <400> 274
His Leu Arg Ile Leu Arg Asp Ser Arg Thr His Ser Tyr Phe Leu Thr
  1      5      10      15
Ser Leu Arg Gly Glu Asn Asn Pro Trp Thr Asp Gln Ser Pro Cys Ala
      20      25      30
Ala Ala Ser Arg Ala Gln His Leu His Pro Ala Ala Val Ala Ala Ala
      35      40      45
Thr Met Pro Lys Thr Lys Ala Glu Gly Asp Ala Lys Gly Asp Lys Ala
      50      55      60
Lys Val Lys Asp Glu Pro Gln Val Thr Arg Ala Ala Ile Gln Thr Asn
      65      70      75      80
Thr Phe Ile Phe Lys Cys Xaa Ile Glu Pro Gln Lys Gln Ile Tyr Ile
      85      90      95
Leu Tyr Ile Gln Asn Ser Cys Gln Ile Ser Leu Leu Ile Leu Pro Lys
      100      105      110
Ser Thr Leu Met Lys Trp Met Gln Thr Leu
      115      120

```

```

<210> 275
<211> 630
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(630)
<223> Xaa = X or * as defined in Table 6

```

<400> 275

Ser	Ser	Val	Glu	Gln	Ala	Ser	Val	Glu	Val	Pro	Asp	Gly	Pro	Thr	Leu
1				5					10					15	
His	Asp	Pro	Asp	Leu	Tyr	Ile	Glu	Ile	Val	Lys	Asn	Thr	Lys	Ser	Val
			20					25					30		
Pro	Glu	Tyr	Ser	Glu	Val	Ala	Tyr	Pro	Asp	Tyr	Phe	Gly	His	Ile	Pro
		35					40					45			
Pro	Pro	Phe	Lys	Glu	Pro	Ile	Leu	Glu	Arg	Pro	Tyr	Gly	Val	Gln	Arg
	50					55					60				
Thr	Lys	Ile	Ala	Gln	Asp	Ile	Glu	Arg	Leu	Ile	His	Gln	Ser	Asp	Ile
65					70					75					80
Ile	Asp	Arg	Val	Val	Tyr	Asp	Leu	Asp	Asn	Pro	Asn	Tyr	Thr	Ile	Pro
			85						90					95	
Glu	Glu	Gly	Asp	Ile	Leu	Lys	Phe	Asn	Ser	Lys	Phe	Glu	Ser	Gly	Asn
			100					105					110		
Leu	Arg	Arg	Val	Ile	Gln	Ile	Arg	Lys	Asn	Glu	Tyr	Asp	Leu	Ile	Leu
	115						120					125			
Asn	Ser	Asp	Ile	Asn	Ser	Asn	His	Tyr	His	Gln	Trp	Phe	Tyr	Phe	Glu
	130					135					140				
Val	Ser	Gly	Met	Arg	Pro	Gly	Val	Ala	Tyr	Arg	Phe	Asn	Ile	Ile	Asn
145					150					155					160
Cys	Glu	Arg	Cys	Asn	Arg	Leu	Phe	Asn	Tyr	Gly	Met	Gln	Pro	Leu	Met
			165						170					175	
Tyr	Ser	Val	Gln	Glu	Ala	Leu	Asn	Ala	Arg	Pro	Trp	Trp	Ile	Arg	Met
		180						185					190		
Gly	Thr	Asp	Ile	Arg	Tyr	Tyr	Ile	Asn	His	Phe	Ser	Arg	Ser	Ser	Val
	195						200					205			
Ala	Ala	Gly	Gly	Ala	Gln	Arg	Gly	Lys	Ser	Tyr	Tyr	Thr	Ile	Thr	Phe
	210					215					220				
Thr	Val	Gln	Phe	Ser	Thr	Xaa	Arg	Met	Asp	Val	Cys	Tyr	Phe	Ala	Tyr
225					230					235					240
Ile	His	Tyr	Pro	Tyr	Thr	Tyr	Ser	Thr	Leu	Gln	Met	His	Leu	Gln	Lys
			245						250					255	
Leu	Glu	Ser	Ala	His	Asn	Pro	Gln	Gln	Ile	Tyr	Phe	Arg	Lys	Asp	Val
		260						265					270		
Leu	Cys	Glu	Thr	Leu	Ser	Gly	Asn	Ser	Cys	Pro	Leu	Val	Thr	Ile	Thr
	275						280					285			
Ala	Met	Pro	Glu	Ser	Asn	Tyr	Tyr	Glu	His	Ile	Cys	His	Phe	Arg	Asn
	290					295					300				
Arg	Pro	Tyr	Val	Leu	Met	Tyr	Ala	Arg	Val	His	Pro	Gly	Glu	Thr	Asn
305					310					315					320
Ala	Ser	Trp	Gly	Tyr	Glu	Arg	Glu	Arg	Trp	Glu	Tyr	Leu	His	Glu	Ala
			325						330					335	
Ile	Asn	Pro	Thr	Gly	Phe	Arg	Ser	Leu	Arg	Arg	Asn	Leu	Tyr	Tyr	Ile
		340						345					350		
Phe	Lys	Ile	Val	Pro	Met	Leu	Asn	Pro	Asp	Gly	Val	Ile	Asn	Gly	Asn
	355						360					365			
His	Arg	Cys	Ser	Leu	Ser	Gly	Glu	Asp	Leu	Asn	Arg	Gln	Trp	Gln	Ser
	370					375					380				
Pro	Ser	Pro	Asp	Leu	His	Pro	Thr	Ile	Tyr	His	Ala	Lys	Gly	Leu	Leu
385					390					395					400
Gln	Tyr	Leu	Ala	Ala	Val	Lys	Arg	Leu	Pro	Leu	Val	Tyr	Cys	Asp	Tyr
			405						410					415	
His	Gly	His	Ser	Arg	Lys	Lys	Asn	Val	Phe	Met	Tyr	Gly	Cys	Ser	Ile
		420						425					430		
Lys	Glu	Thr	Val	Trp	His	Thr	Asn	Asp	Asn	Ala	Thr	Ser	Cys	Asp	Val
		435					440					445			
Val	Glu	Asp	Thr	Gly	Tyr	Arg	Thr	Leu	Pro	Lys	Ile	Leu	Ser	His	Ile
	450					455					460				
Ala	Pro	Ala	Phe	Cys	Met	Ser	Ser	Cys	Ser	Phe	Val	Val	Glu	Lys	Ser
465					470					475					480
Lys	Glu	Ser	Thr	Ala	Arg	Val	Val	Val	Xaa	Arg	Glu	Ile	Gly	Val	Gln
			485						490					495	
Arg	Ser	Tyr	Thr	Met	Glu	Ser	Thr	Leu	Cys	Gly	Cys	Asp	Gln	Gly	Lys

```

          500          505          510
Tyr Lys Gly Leu Gln Ile Gly Thr Arg Glu Leu Glu Glu Met Gly Ala
          515          520          525
Lys Phe Cys Val Gly Leu Leu Arg Leu Lys Arg Leu Thr Ser Pro Leu
          530          535          540
Glu Tyr Asn Pro Ala Leu Pro Ser Pro Ala Leu Thr Phe Glu Asn Asp
545          550          555          560
Leu Asn Xaa Ile Gln Ala Cys Lys Val Thr Ser Pro Tyr Pro Leu Met
          565          570          575
Ser Leu Asp Glu Asp Glu Pro Arg Phe Leu Glu Glu Val Asp Tyr Ser
          580          585          590
Ala Glu Ser Asn Asp Glu Leu Asp Ile Glu Leu Ala Glu Asn Val Gly
          595          600          605
Asp Tyr Glu Pro Ser Ala Gln Glu Glu Val Leu Ser Asp Ser Glu Leu
          610          615          620
Ser Arg Thr Tyr Leu Pro
625          630

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<210> 276
<211> 812
<212> PRT
<213> Homo sapiens

```

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<220>
<221> misc_feature
<222> (1)...(812)
<223> Xaa = X or * as defined in Table 6

```

```

          <400> 276
Ile Lys Ala Leu Ser Ser Ser Ala Glu Asp Ala Ser Leu Val Asn Ala
  1          5          10          15
Ser Ile Ser Ser Ser Val Lys Ala Thr Ser Pro Val Lys Ser Thr Thr
          20          25          30
Ser Ile Thr Asp Ala Lys Ser Cys Glu Gly Gln Asn Pro Glu Leu Leu
          35          40          45
Pro Lys Thr Pro Ile Ser Pro Leu Lys Thr Gly Val Ser Lys Pro Ile
          50          55          60
Val Lys Ser Thr Leu Ser Gln Thr Val Pro Ser Lys Gly Glu Leu Ser
          65          70          75          80
Arg Glu Ile Cys Leu Gln Ser Gln Ser Lys Asp Lys Ser Thr Thr Pro
          85          90          95
Gly Gly Thr Gly Ile Lys Pro Phe Leu Glu Arg Phe Gly Glu Arg Cys
          100          105          110
Gln Glu His Ser Lys Glu Ser Pro Ala Arg Ser Thr Pro His Arg Thr
          115          120          125
Pro Ile Ile Thr Pro Asn Thr Lys Ala Ile Gln Glu Arg Leu Phe Lys
          130          135          140
Gln Asp Thr Ser Ser Ser Thr Thr His Leu Ala Gln Gln Leu Lys Gln
          145          150          155          160
Glu Arg Gln Lys Glu Leu Ala Cys Leu Arg Gly Arg Phe Asp Lys Gly
          165          170          175
Asn Ile Trp Ser Ala Glu Lys Gly Gly Asn Ser Lys Ser Lys Gln Leu
          180          185          190
Glu Thr Lys Gln Glu Thr His Cys Gln Ser Thr Pro Leu Lys Lys His
          195          200          205
Gln Gly Val Ser Lys Thr Gln Ser Leu Pro Val Thr Glu Lys Val Thr
          210          215          220
Glu Asn Gln Ile Pro Ala Lys Asn Ser Ser Thr Glu Pro Lys Glu Val
          225          230          235          240
Ile Arg Glu Ile Glu Met Ser Val Asp Asp Asp Asp Ile Asn Ser Ser
          245          250          255

```

Lys Val Ile Asn Asp Leu Phe Ser Asp Val Leu Glu Glu Gly Glu Leu
 260 265 270
 Asp Met Glu Lys Ser Gln Ala Gly Asp Gly Ser Ser Ile Ser Arg Thr
 275 280 285
 Ala Ala Lys Asn Arg Lys Met His Xaa Ile Ser Pro Gln Cys Leu Tyr
 290 295 300
 Leu His His Trp His Lys Gln Leu Val Xaa Val Xaa Cys Pro His Leu
 305 310 315 320
 Asp Trp Asn Xaa Lys Thr Pro Ala Glu Val Met Lys Val Gln Asn Gln
 325 330 335
 Glu Asn Ser Lys Glu Leu Val Ser Arg Arg Ala Glu Ser Gly Asp Ser
 340 345 350
 Leu Gly Ser Glu Asp Arg Asp Leu Leu Tyr Arg Ser Gln Arg Phe Lys
 355 360 365
 Glu Thr Glu Arg Pro Ser Ile Lys Gln Val Ile Val Arg Lys Glu Asp
 370 375 380
 Val Thr Ser Lys Leu Asp Glu Lys Asn Asn Ala Phe Pro Cys Gln Val
 385 390 395 400
 Asn Ile Lys Gln Lys Met Gln Glu Leu Asn Asn Glu Ile Asn Met Gln
 405 410 415
 Gln Thr Val Ile Tyr Gln Ala Ser Gln Ala Leu Asn Cys Cys Val Asp
 420 425 430
 Glu Glu His Gly Lys Gly Ser Leu Glu Glu Ala Glu Ala Glu Arg Leu
 435 440 445
 Leu Leu Ile Ala Thr Gly Lys Arg Thr Leu Leu Ile Asp Glu Leu Asn
 450 455 460
 Lys Leu Lys Asn Glu Gly Pro Gln Arg Lys Asn Xaa Gly Xaa Ser Ala
 465 470 475 480
 Pro Ser Glu Phe Ile Ala Ile Pro Lys Asp Gln Phe Thr Leu Ser Glu
 485 490 495
 Ile Arg Leu Pro Xaa Lys Ala Asp Phe Val Cys Ser Thr Val Gln Lys
 500 505 510
 Pro Asp Ala Ala Asn Tyr Tyr Tyr Leu Ile Ile Leu Lys Ser Arg Ser
 515 520 525
 Glu Asn Met Val Ala Thr Pro Leu Ala Ser Thr Ser Asn Ser Leu Asn
 530 535 540
 Gly Asp Ala Leu Thr Phe Thr Thr Thr Phe Thr Leu Gln Asp Val Ser
 545 550 555 560
 Asn Asp Phe Glu Ile Asn Ile Glu Val Tyr Ser Leu Val Gln Lys Lys
 565 570 575
 Asp Pro Ser Gly Leu Asp Lys Lys Lys Thr Ser Lys Ser Lys Lys
 580 585 590
 Ser Asn Ile His Ser Ser Val Met Ala Ser Pro Gly Gly Leu Ser Ala
 595 600 605
 Val Arg Thr Ser Asn Phe Ala Leu Val Gly Ser Tyr Thr Leu Ser Leu
 610 615 620
 Ser Ser Val Gly Asn Thr Lys Phe Val Leu Asp Lys Val Pro Phe Leu
 625 630 635 640
 Ser Ser Leu Glu Gly His Ile Tyr Leu Lys Ile Lys Cys Gln Val Asn
 645 650 655
 Ser Ser Val Glu Glu Arg Gly Phe Leu Gly Cys Pro Gly Gly Gly Arg
 660 665 670
 Leu Gln Pro Lys Arg Gln Thr Ile Phe Glu Asp Val Ser Gly Phe Gly
 675 680 685
 Ala Trp His Arg Arg Trp Cys Val Leu Ser Gly Asn Cys Ile Ser Tyr
 690 695 700
 Trp Thr Tyr Pro Asp Asp Glu Lys Arg Lys Asn Pro Ile Gly Arg Ile
 705 710 715 720
 Asn Leu Ala Asn Cys Thr Ser Arg Gln Ile Glu Pro Ala Asn Arg Glu
 725 730 735
 Phe Cys Ala Arg Arg Asn Thr Phe Glu Leu Ile Thr Val Arg Pro Gln
 740 745 750
 Arg Glu Asp Asp Arg Glu Thr Leu Val Thr Asn Ala Gly Thr His Ser
 755 760 765

Val Phe Thr Lys Asn Trp Leu Ser Ala Asp Thr Lys Glu Glu Arg Asp
 770 775 780
 Leu Trp Met Gln Lys Leu Asn Gln Val Leu Cys Asp Ile Arg Leu Trp
 785 790 795 800
 Gln Pro Asp Ala Cys Tyr Lys Pro Ile Gly Lys Pro
 805 810

<210> 277
 <211> 772
 <212> PRT
 <213> Homo sapiens

<400> 277
 Met Gln Ile Asn Glu Thr Ile Trp Asp Thr Val Gly Ala Ala Ser Arg
 1 5 10 15
 His Gly Glu Gly Glu Arg Gln Ala Lys Ser Ser Thr Arg Gly Cys Thr
 20 25 30
 His Leu Ala Glu Gly Gln Gly Ile Tyr Leu Gln Glu Glu Gln Ser Pro
 35 40 45
 Pro Glu Met Cys Thr Arg Val Met Glu Lys Arg Glu Gly Leu Thr Ile
 50 55 60
 Glu Arg Glu Arg Asp Pro Leu Leu Pro Val Trp Lys Ala Leu Gly Ile
 65 70 75 80
 Gln Ala His Lys Cys Val Ala His Thr Thr Asn Pro Ser Lys Ala Thr
 85 90 95
 Ala Val His Leu Pro His Leu Thr Met Gln Pro Gln Gly Cys Leu Met
 100 105 110
 Ser Phe Phe Pro Thr Ala Ala Glu Phe Ser Thr Tyr Gly Gln Glu Leu
 115 120 125
 Tyr Leu Glu Asn Asn Gln Ile Glu Glu Ile Thr Glu Ile Cys Phe Asn
 130 135 140
 His Thr Arg Lys Ile Asn Val Ile Val Leu Arg Tyr Asn Lys Ile Glu
 145 150 155 160
 Glu Asn Arg Ile Ala Pro Leu Ala Trp Ile Asn Gln Glu Asn Leu Glu
 165 170 175
 Ser Ile Asp Leu Ser Tyr Asn Lys Leu Tyr His Val Pro Ser Tyr Leu
 180 185 190
 Pro Lys Ser Leu Leu His Leu Val Leu Leu Gly Asn Gln Ile Glu Arg
 195 200 205
 Ile Pro Gly Tyr Val Phe Gly His Met Glu Pro Gly Leu Glu Tyr Leu
 210 215 220
 Tyr Leu Ser Phe Asn Lys Leu Ala Asp Asp Gly Met Asp Arg Val Ser
 225 230 235 240
 Phe Tyr Gly Ala Tyr His Ser Leu Arg Glu Leu Phe Leu Asp His Asn
 245 250 255
 Asp Leu Lys Ser Ile Pro Pro Gly Ile Gln Glu Met Lys Ala Leu His
 260 265 270
 Phe Leu Arg Leu Asn Asn Asn Lys Ile Arg Gly Asn Lys Gln Glu Ile
 275 280 285
 Lys Gln Thr Ser Lys Gln Ala Ser Ala Val Gln Ser Glu Lys Trp Val
 290 295 300
 Thr Met Arg Arg Ala His Trp Gly Leu Arg Ala Ala Arg Arg Leu Arg
 305 310 315 320
 Pro Pro Ser Thr Ala Trp Ile Asn Ser Arg Ser Arg Pro Val Pro Val
 325 330 335
 Glu Gln Thr His Cys Gly Leu Ala Val Ala Glu Glu Arg Lys Asp Leu
 340 345 350
 Phe Met Phe Phe Arg Ser Leu His Phe Phe Val Glu Trp Phe Glu Tyr
 355 360 365
 Arg Lys Arg Thr Phe Lys His Leu Lys Trp Asp Glu Asp Tyr Asp Gln
 370 375 380

Glu Pro Asp Asp Asp Tyr Gln Thr Gly Phe Pro Phe Arg Gln Asn Val
 385 390 395 400
 Asp Tyr Gly Val Pro Phe His Gln Tyr Thr Leu Gly Cys Val Ser Glu
 405 410 415
 Cys Phe Cys Pro Thr Asn Phe Pro Ser Ser Met Tyr Cys Asp Asn Arg
 420 425 430
 Lys Leu Lys Thr Ile Pro Asn Ile Pro Met His Ile Gln Gln Leu Tyr
 435 440 445
 Leu Gln Phe Asn Glu Ile Glu Ala Val Thr Ala Asn Ser Phe Ile Asn
 450 455 460
 Ala Thr His Leu Lys Glu Ile Asn Leu Ser His Asn Lys Ile Lys Ser
 465 470 475 480
 Gln Lys Ile Asp Tyr Gly Val Phe Ala Lys Leu Pro Asn Leu Leu Gln
 485 490 495
 Leu His Leu Glu His Asn Asn Leu Glu Glu Phe Pro Phe Pro Leu Pro
 500 505 510
 Lys Ser Leu Glu Arg Leu Leu Leu Gly Tyr Asn Glu Ile Ser Lys Leu
 515 520 525
 Gln Thr Asn Ala Met Asp Gly Leu Val Asn Leu Thr Met Leu Asp Leu
 530 535 540
 Cys Tyr Asn Tyr Leu His Asp Ser Leu Leu Lys Asp Lys Ile Phe Ala
 545 550 555 560
 Lys Met Glu Lys Leu Met Gln Leu Asn Leu Cys Ser Asn Arg Leu Glu
 565 570 575
 Ser Met Pro Pro Gly Leu Pro Ser Ser Leu Met Tyr Leu Ser Leu Glu
 580 585 590
 Asn Asn Ser Ile Ser Ser Ile Pro Glu Lys Tyr Phe Asp Lys Leu Pro
 595 600 605
 Lys Leu His Thr Leu Arg Met Ser His Asn Lys Leu Gln Asp Ile Pro
 610 615 620
 Tyr Asn Ile Phe Asn Leu Pro Asn Ile Val Glu Leu Ser Val Gly His
 625 630 635 640
 Asn Lys Leu Lys Gln Ala Phe Tyr Ile Pro Arg Asn Leu Glu His Leu
 645 650 655
 Tyr Leu Gln Asn Asn Glu Ile Glu Lys Met Asn Leu Thr Val Met Cys
 660 665 670
 Pro Ser Ile Asp Pro Leu His Tyr His His Leu Thr Tyr Ile Arg Val
 675 680 685
 Asp Gln Asn Lys Leu Lys Glu Pro Ile Ser Ser Tyr Ile Phe Phe Cys
 690 695 700
 Phe Pro His Ile His Thr Ile Tyr Tyr Gly Glu Gln Arg Ser Thr Asn
 705 710 715 720
 Gly Gln Thr Ile Gln Leu Lys Thr Gln Val Phe Arg Arg Phe Pro Asp
 725 730 735
 Asp Asp Asp Glu Ser Glu Asp His Asp Asp Pro Asp Asn Ala His Glu
 740 745 750
 Ser Pro Glu Gln Glu Gly Ala Glu Gly His Phe Asp Leu His Tyr Tyr
 755 760 765
 Glu Asn Gln Glu
 770

<210> 278

<211> 65

<212> PRT

<213> Homo sapiens

<400> 278

Ser Arg Arg Arg Gly Gly Val Ser Ala Pro Thr Ser Phe Tyr Gly Arg
 1 5 10 15
 Asp Arg Arg Met Phe Pro Ala Gln Glu Glu Ala Asp Arg Thr Val Phe
 20 25 30

Val Gly Asn Leu Glu Ala Arg Val Arg Glu Glu Ile Leu Tyr Glu Leu
 35 40 45
 Phe Leu Gln Val Leu Cys Pro Arg Glu Met Gly Ile Leu Ser Ile Ser
 50 55 60
 Pro
 65

<210> 279
 <211> 294
 <212> PRT
 <213> Homo sapiens

<400> 279
 Met Ser Arg Trp Gly Ala Ala Val Gly Gln Gly Ala Leu Arg Glu Glu
 1 5 10 15
 His Phe Ala His Ala His Ile Thr Glu Arg Thr Arg Arg Val Arg Glu
 20 25 30
 Gly Arg Arg Lys Arg Arg Ser Ser Leu Leu Thr Thr Ser Pro Thr Ser
 35 40 45
 Ala Asn Ala Gln Ala His Phe Leu Lys Leu Lys Val Ser Ile Asp Lys
 50 55 60
 Gly Pro Gln Asn Arg Ala Gly Ala Ile Val Pro Trp Phe Ala Lys Met
 65 70 75 80
 Ser Phe Pro Lys Tyr Lys Pro Ser Ser Leu Arg Thr Leu Pro Glu Thr
 85 90 95
 Leu Asp Pro Ala Glu Tyr Asn Ile Ser Pro Glu Thr Arg Arg Ala Gln
 100 105 110
 Ala Glu Arg Leu Ala His Arg Ala Gln Leu Lys Arg Glu Tyr Leu Leu
 115 120 125
 Gln Tyr Asn Asp Pro Asn Arg Arg Gly Leu Ile Glu Asn Pro Ala Leu
 130 135 140
 Leu Arg Trp Ala Tyr Ala Arg Thr Ile Asn Val Tyr Pro Asn Phe Lys
 145 150 155 160
 Pro Thr Pro Lys Ser Ser Leu Met Gly Ala Phe Val Trp Asp Phe Gly
 165 170 175
 Pro Leu Ile Phe Ile Tyr Tyr Ile Ile Lys Thr Glu Arg Trp Asp Pro
 180 185 190
 Asn Gln Arg Trp Leu Thr Asp Ser Arg Ile Leu Lys Tyr Glu Ala Ile
 195 200 205
 Leu Leu Glu Arg Asp Asp Leu Thr Leu Thr Thr Asp Asn Ser Leu Asn
 210 215 220
 Pro Ala Ala Phe Leu Arg Gly Asn Pro Asn Pro Glu Glu Pro Glu His
 225 230 235 240
 Lys Cys Leu Asp Leu Ile Ser Tyr Gln Thr Arg Val Arg Leu Asp Leu
 245 250 255
 Ser Lys Thr Pro Phe Gln Thr Gly Arg His Leu Phe Ile Asp Gly Ser
 260 265 270
 Ser Leu Val Ile Gly Gly Lys Gly His Asn Gly Tyr Ser Val Val Asp
 275 280 285
 Gly Glu Thr Leu Thr Lys
 290

<210> 280
 <211> 198
 <212> PRT
 <213> Homo sapiens

<400> 280

```

Met Gln Thr Phe Thr Thr Cys Ile Ser Tyr Ser Glu Tyr Ser Cys Met
 1          5          10          15
Leu Leu Ala Asn Ala Ser Ser His Gly Thr Leu Tyr Cys Lys Leu Arg
          20          25          30
Val Gly Ile Cys Leu Leu Met Val Pro Ala Val Lys Asn Gln Ala Ser
          35          40          45
Gly Ser Ala Arg Gly Ala Thr Lys Val Arg Arg Lys Cys Gln Ala Gly
          50          55          60
Cys Gln Asn Glu His Leu Gly Glu Leu Asp Asp Gly Thr Asp Gly Lys
          65          70          75          80
Asn Gln Leu Asn Ile Arg Glu Asn Gly Gly Arg Gly Gln Asn Cys Glu
          85          90          95
Gln Glu Leu Glu Glu Ser Val Ala Glu Lys Asp Leu Ser Gln Thr Ser
          100          105          110
Arg Asp Leu Glu Lys Met Met Ser Lys His Ile Phe Leu Lys Pro Met
          115          120          125
Leu Ser Ile Ser Asp Leu Val Asn Phe Leu Met Gln Val Ser Lys Val
          130          135          140
Leu Val Lys Thr Ala Glu Gly Ile Val Leu Gln Gln Leu Pro Leu Ala
          145          150          155          160
Phe Pro Ala Leu His Phe His Ala Tyr Gly Asn Leu Phe Pro Val Cys
          165          170          175
Ser Phe Lys His Tyr Ile Tyr Met Ile Asp His Pro Ile Phe Ile Ser
          180          185          190
Ile Pro Asp Phe Leu Thr
          195

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<210> 281
<211> 1352
<212> PRT
<213> Homo sapiens

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```

<400> 281
Met Pro Val Pro Ser Arg His Ile Asn Ile Gly Arg Ser Gln Ser Trp
 1          5          10          15
Asp Ala Ala Gly Trp Tyr Glu Gly Pro Trp Glu Asn Ala Glu Ser Leu
          20          25          30
Arg Pro Leu Gly Arg Arg Ser Ser Leu Thr Tyr Gly Thr Ala Glu Gly
          35          40          45
Thr Trp Phe Glu Pro Asn His Arg Pro Gln Asp Ala Ala Leu Pro Val
          50          55          60
Ala Ala Glu Pro Tyr Leu Tyr Arg Glu Ala Val Tyr Asn Ser Val Ala
          65          70          75          80
Ala Arg Lys Gly Ser Thr Pro Asp Phe Thr Phe Tyr Asp Ser Arg Gln
          85          90          95
Ala Val Met Ser Gly Arg Ser Pro Leu Leu Pro Arg Glu Tyr Tyr Ser
          100          105          110
Asp Pro Ser Gly Ala Ala Arg Val Pro Lys Glu Pro Pro Leu Tyr Arg
          115          120          125
Asp Pro Gly Val Ser Arg Pro Val Pro Ser Tyr Gly Val Leu Gly Ser
          130          135          140
Arg Thr Ser Trp Asp Pro Met Gln Gly Arg Ser Pro Ala Leu Gln Asp
          145          150          155          160
Ala Gly His Leu Tyr Arg Asp Pro Gly Gly Lys Met Ile Pro Gln Gly
          165          170          175
Arg Gln Thr Gln Ser Arg Ala Ala Ser Pro Gly Arg Tyr Gly Arg Glu
          180          185          190
Gln Pro Asp Thr Arg Tyr Gly Ala Glu Val Pro Ala Tyr Pro Leu Ser
          195          200          205
Gln Val Phe Ser Asp Ile Ser Glu Arg Pro Ile Asp Pro Ala Pro Ala
          210          215          220

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Arg Gln Val Ala Pro Thr Cys Leu Val Val Asp Pro Ser Ser Ala Ala
 225 230 235 240
 Ala Pro Glu Gly Ser Thr Gly Val Ala Pro Gly Ala Leu Asn Arg Gly
 245 250 255
 Tyr Gly Pro Ala Arg Glu Ser Ile Pro Ser Lys Met Ala Tyr Glu Thr
 260 265 270
 Tyr Glu Ala Asp Leu Ser Thr Phe Gln Gly Pro Gly Gly Lys Arg Thr
 275 280 285
 Val Leu Pro Glu Phe Leu Ala Phe Leu Arg Ala Glu Gly Leu Ala Glu
 290 295 300
 Ala Thr Leu Gly Ala Leu Leu Gln Gln Gly Phe Asp Ser Pro Ala Val
 305 310 315 320
 Leu Ala Thr Leu Glu Asp Ala Asp Ile Lys Ser Val Ala Pro Asn Leu
 325 330 335
 Gly Gln Ala Arg Val Leu Ser Arg Leu Ala Asn Ser Cys Arg Thr Glu
 340 345 350
 Met Gln Leu Arg Arg Gln Asp Arg Gly Gly Pro Leu Pro Arg Ala Arg
 355 360 365
 Ser Ser Ser Phe Ser His Arg Ser Glu Leu Leu His Gly Asp Leu Ala
 370 375 380
 Ser Leu Gly Ala Ala Ala Pro Leu Gln Thr Ala Ser Pro Arg Ala Gly
 385 390 395 400
 Asp Pro Ala Arg Arg Pro Ser Ser Ala Pro Ser Gln His Leu Leu Glu
 405 410 415
 Thr Ala Ala Thr Tyr Ser Ala Pro Gly Val Gly Thr His Ala Pro His
 420 425 430
 Phe Pro Ser Asn Ser Gly Tyr Ser Ser Pro Thr Pro Cys Ala Leu Thr
 435 440 445
 Ala Arg Leu Ser Pro Thr Tyr Pro Leu Gln Ala Gly Val Ala Leu Thr
 450 455 460
 Asn Pro Gly Pro Ser Asn Pro Leu His Pro Gly Pro Arg Thr Ala Tyr
 465 470 475 480
 Ser Thr Ala Tyr Thr Val Pro Met Glu Leu Leu Lys Arg Glu Arg Asn
 485 490 495
 Val Ala Ala Ser Pro Leu Pro Ser Pro His Gly Ser Pro Gln Val Leu
 500 505 510
 Arg Lys Pro Gly Ala Pro Leu Gly Pro Ser Thr Leu Pro Pro Ala Ser
 515 520 525
 Gln Ser Leu His Thr Pro His Ser Pro Tyr Gln Lys Val Ala Arg Arg
 530 535 540
 Thr Gly Ala Pro Ile Ile Val Ser Thr Met Leu Ala Pro Glu Pro Ile
 545 550 555 560
 Gln Phe Ala Gly Gln Ala Val Gln Ser Asp Asn Val Arg Lys Ala Tyr
 565 570 575
 Ala Ala Gly Thr Pro Val Arg Pro Thr Ser Pro Gly Asp Thr Asp Lys
 580 585 590
 Trp Gly Leu Gln Ala Arg Ala Pro Gly Arg Ala Val Asp Pro Arg Asn
 595 600 605
 Met Ile Ser Ala Gln Glu His Lys Val Val Glu Cys Met Ala Arg Arg
 610 615 620
 Ser Ala Thr Cys Phe Val Phe Gly Gln Leu Cys Arg Leu His Ser Thr
 625 630 635 640
 Ser Ser Asp Pro Val Gly Val Asp Phe Ile Leu Ser Met Glu Asp Val
 645 650 655
 Gly Arg Gly Lys Ser Arg Asn Pro Asp Ser Trp Ser Pro Asn Ala Val
 660 665 670
 Val Trp Asp Ala Ser Gly Val Gly Gly Glu Arg Val Leu Gln Tyr Gln
 675 680 685
 Leu Asp Met Asn Thr Val Pro Pro Gln Gly Trp Thr Thr Arg Lys Thr
 690 695 700
 Arg Val Cys Cys Lys His Glu Ala Ser Pro Ser Pro Ile Ser Ala Leu
 705 710 715 720
 Ala Ala Ile Ala Lys Glu Glu Gly Val Ile Leu Leu Leu Trp Thr Phe
 725 730 735

Thr Leu Gly Asn Lys Arg Leu Gly Gly Ser Ala Thr Arg Val Gly Tyr
 740 745 750
 Ala Glu Ala Gln Ala Glu Ala Pro Ser Cys Lys Ala Thr Val Thr
 755 760 765
 Leu Ser Ser Gly Ser Ser His Glu Cys Asp Ser Ser Val Ser Ser Lys
 770 775 780
 Thr Ala Thr Cys Arg Asp Phe Met Gly Gln Pro Trp Gly His Ala Ser
 785 790 795 800
 Ile Pro Pro Thr Pro Asn Pro Pro Pro Ala Val Val Pro Gly Ile
 805 810 815
 Phe Ser Gln His Glu Asn Pro Leu Ala Phe Leu Phe Ser Arg Leu Ala
 820 825 830
 Met Lys Asp Leu Leu Pro Gly Phe Glu Pro Gln Thr Leu Asp Arg Ser
 835 840 845
 Arg Ala Ser Leu Ser His Val Leu Arg Ala Arg Pro Ser Gly Arg Val
 850 855 860
 Glu Gly Ile Arg Pro Gln Ile Met Asn Gly Pro Leu His Pro Arg Pro
 865 870 875 880
 Leu Val Ala Leu Leu Asp Gly Arg Asp Cys Thr Val Glu Met Pro Ile
 885 890 895
 Leu Lys Asp Leu Ala Thr Val Ala Phe Cys Asp Ala Gln Ser Thr Gln
 900 905 910
 Glu Ile His Glu Lys Val Leu Asn Glu Ala Val Gly Ala Met Met Tyr
 915 920 925
 His Thr Ile Thr Leu Thr Arg Glu Asp Leu Glu Lys Phe Lys Ala Leu
 930 935 940
 Arg Val Ile Val Arg Ile Gly Ser Gly Tyr Asp Asn Val Asp Ile Lys
 945 950 955 960
 Ala Ala Gly Glu Leu Gly Glu Cys Glu Ala Ala Leu Ala Ala Trp Ser
 965 970 975
 Cys Pro Glu Leu Cys Gly Pro Cys Ser Gly Gly Leu Gly Glu Ala Ala
 980 985 990
 Gly Thr Gly Thr Thr Glu Gln Pro Leu Leu Ala Val Ala Arg Trp Leu
 995 1000 1005
 Pro Pro Gly Arg Ala Val Glu His Leu Ala Ala Leu Pro Ser His Asp
 1010 1015 1020
 Thr Gly Ile Ala Val Cys Asn Ile Pro Ser Ala Ala Val Glu Glu Thr
 1025 1030 1035 1040
 Ala Asp Ser Thr Ile Cys His Ile Leu Asn Leu Tyr Arg Arg Asn Thr
 1045 1050 1055
 Trp Leu Tyr Gln Ala Leu Arg Glu Gly Thr Arg Val Gln Ser Val Glu
 1060 1065 1070
 Gln Ile Arg Glu Val Ala Ser Gly Ala Ala Arg Ile Arg Gly Glu Thr
 1075 1080 1085
 Leu Gly Leu Ile Gly Phe Gly Arg Thr Gly Gln Ala Val Ala Val Arg
 1090 1095 1100
 Ala Lys Ala Phe Gly Phe Ser Val Ile Phe Tyr Asp Pro Tyr Leu Gln
 1105 1110 1115 1120
 Asp Gly Ile Glu Arg Ser Leu Gly Val Gln Arg Val Tyr Thr Leu Gln
 1125 1130 1135
 Asp Leu Leu Tyr Gln Ser Asp Cys Val Ser Leu His Cys Asn Leu Asn
 1140 1145 1150
 Glu His Asn His His Leu Ile Asn Asp Phe Thr Ile Lys Gln Met Arg
 1155 1160 1165
 Ala Gly Ser Ile Pro Leu Trp Asn Ala Ala Arg Gly Gly Leu Val Asp
 1170 1175 1180
 Glu Lys Ala Leu Ala Gln Ala Leu Lys Glu Gly Arg Ile Arg Gly Ala
 1185 1190 1195 1200
 Ala Leu Asp Val His Glu Ser Glu Pro Phe Ser Phe Ala Gln Gly Pro
 1205 1210 1215
 Leu Lys Asp Ala Pro Asn Leu Ile Cys Thr Pro His Thr Ala Trp Tyr
 1220 1225 1230
 Ser Glu Gln Ala Ser Leu Glu Met Arg Glu Ala Ala Ala Thr Glu Ile
 1235 1240 1245

```

Arg Arg Ala Ile Thr Gly Arg Ile Pro Glu Ser Leu Arg Asn Cys Val
1250                      1255                      1260
Asn Lys Glu Phe Phe Val Thr Ser Ala Pro Trp Ser Val Ile Asp Gln
1265                      1270                      1275                      1280
Gln Ala Ile His Pro Glu Leu Asn Gly Ala Thr Tyr Arg Tyr Pro Pro
1285                      1290                      1295
Gly Ile Val Gly Val Ala Pro Gly Gly Leu Pro Ala Ala Met Glu Gly
1300                      1305                      1310
Ile Ile Pro Gly Gly Ile Pro Val Thr His Asn Leu Pro Thr Val Ala
1315                      1320                      1325
His Pro Ser Gln Ala Pro Ser Pro Asn Gln Pro Thr Lys His Gly Asp
1330                      1335                      1340
Asn Arg Glu His Pro Asn Glu Gln
1345                      1350

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<210> 282
<211> 181
<212> PRT
<213> Homo sapiens

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```

<400> 282
Leu Leu Lys Ile Ser Gly Ile Ile Leu Lys Thr Gly Glu Ser Gln Asn
1      5      10      15
Gln Leu Ala Val Asp Gln Ile Ala Phe Gln Lys Lys Leu Phe Gln Thr
20      25      30
Leu Arg Arg His Pro Ser Tyr Pro Lys Ile Ile Glu Glu Phe Val Ser
35      40      45
Gly Leu Glu Ser Tyr Ile Glu Asp Glu Asp Ser Phe Arg Asn Cys Leu
50      55      60
Leu Ser Cys Glu Arg Leu Gln Asp Glu Glu Ala Ser Met Gly Ala Ser
65      70      75      80
Tyr Ser Lys Ser Leu Ile Lys Leu Leu Leu Gly Ile Asp Ile Leu Gln
85      90      95
Pro Ala Ile Ile Lys Thr Leu Phe Glu Lys Leu Pro Glu Tyr Phe Phe
100     105     110
Glu Asn Lys Asn Ser Asp Glu Ile Asn Ile Pro Arg Leu Ile Val Ser
115     120     125
Gln Leu Lys Trp Leu Asp Arg Val Val Asp Gly Lys Asp Leu Thr Thr
130     135     140
Lys Ile Met Gln Leu Ile Ser Ile Ala Pro Glu Asn Leu Gln His Asp
145     150     155     160
Ile Ile Thr Ser Leu Pro Glu Ile Leu Gly Asp Ser Gln His Ala Asp
165     170     175
Val Gly Lys Glu Leu
180

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```

<210> 283
<211> 1385
<212> PRT
<213> Homo sapiens

```

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<220>
<221> misc_feature
<222> (1)...(1385)
<223> Xaa = X or * as defined in Table 6

```

```

<400> 283
Lys Arg Lys Arg Arg Arg Thr Trp Lys Arg Tyr Arg Ser Ile Ile Asp

```

1	5	10	15
His	Leu	Gln	Glu
20	Lys	Arg	Arg
Thr	Leu	Val	Gln
35	Pro	Glu	Ala
Met	Pro	Ile	Tyr
50	Pro	Thr	Tyr
65	Leu	Arg	Pro
80	Leu	Asp	Thr
95	Leu	Arg	Glu
110	Leu	Arg	Glu
125	Ile	Val	Arg
140	Leu	Arg	Glu
155	Leu	Val	Cys
170	Leu	Val	Cys
185	Leu	Val	Cys
200	Leu	Val	Cys
215	Leu	Val	Cys
230	Leu	Val	Cys
245	Leu	Val	Cys
260	Leu	Val	Cys
275	Leu	Val	Cys
290	Leu	Val	Cys
305	Leu	Val	Cys
320	Leu	Val	Cys
335	Leu	Val	Cys
350	Leu	Val	Cys
365	Leu	Val	Cys
380	Leu	Val	Cys
395	Leu	Val	Cys
410	Leu	Val	Cys
425	Leu	Val	Cys
440	Leu	Val	Cys
455	Leu	Val	Cys
470	Leu	Val	Cys
485	Leu	Val	Cys
500	Leu	Val	Cys
510	Leu	Val	Cys

515					520					525					
Asp	Glu	Glu	Glu	Glu	Gly	Glu	Glu	Arg	Glu	Phe	Arg	Leu	Ile	Arg	Asp
530						535					540				
Ser	Gln	Arg	Glu	Ala	Asp	Pro	Asp	Phe	Lys	Gln	Thr	Gly	Xaa	Leu	Arg
545					550					555				560	
Arg	Lys	Arg	Trp	Xaa	Gly	Pro	Ser	Gly	Gly	Arg	Arg	Lys	Arg	Val	Glu
			565					570					575		
Gln	Thr	Arg	Ser	Trp	Leu	Lys	Cys	Phe	Trp	Pro	Xaa	Gly	Xaa	Thr	Ile
			580					585					590		
Val	Ala	Leu	Gly	Gln	Gln	Leu	Asp	Arg	Ser	Lys	Pro	Gln	Glu	Ser	Gly
		595					600					605			
Arg	Pro	Ser	Asp	Asn	Gln	Lys	Lys	Lys	Met	Lys	Lys	Arg	Val	Lys	Asp
610						615					620				
Glu	Leu	Arg	Lys	Leu	Asn	Thr	Met	Thr	Ala	Ala	Glu	Ala	Asn	Glu	Ile
625					630					635				640	
Glu	Asp	Val	Trp	Gln	Leu	Asp	Leu	Ser	Ser	Arg	Trp	Gln	Leu	Tyr	Arg
			645					650					655		
Leu	Trp	Leu	Gln	Leu	Tyr	Gln	Ala	Asp	Thr	Arg	Arg	Lys	Ile	Leu	Ser
		660						665					670		
Tyr	Glu	Arg	Gln	Tyr	Arg	Thr	Ser	Ala	Glu	Arg	Met	Ala	Glu	Leu	Arg
	675					680						685			
Leu	Gln	Glu	Asp	Leu	His	Ile	Leu	Lys	Asp	Ala	Gln	Val	Val	Gly	Met
690						695						700			
Thr	Thr	Thr	Gly	Ala	Ala	Lys	Tyr	Arg	Gln	Ile	Leu	Gln	Lys	Val	Glu
705					710					715					720
Pro	Arg	Ile	Val	Ile	Val	Glu	Glu	Ala	Ala	Glu	Val	Leu	Glu	Ala	His
			725					730					735		
Thr	Ile	Ala	Thr	Leu	Ser	Lys	Ala	Cys	Gln	His	Leu	Ile	Leu	Ile	Gly
		740						745					750		
Asp	His	Gln	Gln	Leu	Arg	Pro	Ser	Ala	Asn	Val	Tyr	Asp	Leu	Ala	Lys
	755						760					765			
Asn	Phe	Asn	Leu	Glu	Val	Ser	Leu	Phe	Glu	Arg	Leu	Val	Lys	Val	Asn
	770					775					780				
Ile	Pro	Phe	Val	Arg	Leu	Asn	Tyr	Gln	His	Arg	Met	Cys	Pro	Glu	Ile
785					790					795				800	
Ala	Arg	Leu	Leu	Thr	Pro	His	Ile	Tyr	Gln	Asp	Leu	Glu	Asn	His	Pro
			805					810						815	
Ser	Val	Leu	Lys	Tyr	Glu	Lys	Ile	Lys	Gly	Val	Ser	Ser	Asn	Leu	Phe
		820						825					830		
Phe	Val	Glu	His	Asn	Phe	Pro	Glu	Gln	Glu	Ser	Lys	Arg	Arg	Lys	Ser
	835					840						845			
His	Gln	Asn	Gln	His	Glu	Ala	His	Asn	Val	Val	Glu	Leu	Cys	Lys	Tyr
	850					855					860				
Phe	Leu	Cys	Gln	Glu	Tyr	Leu	Pro	Ser	Gln	Ile	Thr	Ile	Leu	Thr	Thr
865					870					875				880	
Tyr	Thr	Gly	Gln	Leu	Phe	Cys	Leu	Arg	Lys	Leu	Met	Pro	Ala	Lys	Thr
			885					890					895		
Phe	Ala	Gly	Val	Arg	Val	His	Val	Val	Asp	Lys	Tyr	Gln	Gly	Glu	Glu
		900						905					910		
Asn	Asp	Ile	Ile	Leu	Leu	Ser	Leu	Val	Arg	Ser	Asn	Gln	Glu	Gly	Lys
	915						920					925			
Val	Gly	Phe	Leu	Gln	Ile	Ser	Asn	Arg	Ile	Cys	Val	Ala	Leu	Ser	Arg
	930					935						940			
Ala	Lys	Lys	Gly	Met	Tyr	Cys	Ile	Gly	Asn	Met	Gln	Met	Leu	Ala	Lys
945					950					955				960	
Val	Pro	Leu	Trp	Ser	Lys	Ile	Ile	His	Thr	Leu	Arg	Glu	Asn	Asn	Gln
			965					970					975		
Ile	Gly	Pro	Met	Leu	Arg	Leu	Cys	Cys	Gln	Asn	His	Pro	Glu	Thr	His
		980						985					990		
Thr	Leu	Val	Ser	Lys	Ala	Ser	Asp	Phe	Gln	Lys	Val	Pro	Glu	Gly	Gly
	995					1000						1005			
Cys	Ser	Leu	Pro	Cys	Glu	Phe	Arg	Leu	Gly	Cys	Gly	His	Val	Cys	Thr
	1010				1015					1020					
Arg	Ala	Cys	His	Pro	Tyr	Asp	Ser	Ser	His	Lys	Glu	Phe	Gln	Cys	Met

1025 1030 1035 1040
 Lys Pro Cys Gln Lys Val Ile Cys Gln Glu Gly His Arg Cys Pro Leu
 1045 1050 1055
 Val Cys Phe Gln Glu Cys Gln Pro Cys Gln Val Lys Val Pro Lys Thr
 1060 1065 1070
 Ile Pro Arg Cys Gly His Glu Gln Met Val Pro Cys Ser Val Pro Glu
 1075 1080 1085
 Ser Asp Phe Cys Cys Gln Glu Pro Cys Ser Lys Ser Leu Arg Cys Gly
 1090 1095 1100
 His Arg Cys Ser His Pro Cys Gly Glu Asp Cys Val Gln Leu Cys Ser
 1105 1110 1115 1120
 Glu Met Val Thr Ile Lys Leu Lys Cys Gly His Ser Gln Pro Val Lys
 1125 1130 1135
 Cys Gly His Val Glu Gly Leu Leu Tyr Gly Gly Leu Leu Val Lys Cys
 1140 1145 1150
 Thr Thr Lys Cys Gly Thr Ile Leu Asp Cys Gly His Pro Cys Pro Gly
 1155 1160 1165
 Ser Cys His Ser Cys Phe Glu Gly Arg Phe His Glu Arg Cys Gln Gln
 1170 1175 1180
 Pro Cys Lys Arg Leu Leu Ile Cys Ser His Lys Cys Gln Lys Pro Cys
 1185 1190 1195 1200
 Ile Gly Glu Cys Pro Pro Cys Gln Arg Thr Cys Gln Asn Arg Cys Val
 1205 1210 1215
 His Ser Gln Cys Lys Lys Lys Cys Glu Glu Leu Cys Ser Pro Cys Val
 1220 1225 1230
 Glu Pro Met Cys Ser Arg Cys Gln His Tyr Gln Cys Thr Lys Leu Cys
 1235 1240 1245
 Ser Glu Pro Cys Asn Arg Pro Pro Cys Tyr Val Pro Cys Thr Lys Leu
 1250 1255 1260
 Leu Val Cys Gly His Pro Cys Ile Gly Leu Cys Gly Glu Pro Cys Pro
 1265 1270 1275 1280
 Lys Lys Cys Arg Ile Cys His Met Asp Glu Val Thr Gln Ile Phe Phe
 1285 1290 1295
 Gly Phe Glu Asp Glu Pro Asp Ala Arg Phe Val Gln Leu Glu Asp Cys
 1300 1305 1310
 Ser His Ile Phe Glu Val Gln Ala Leu Asp Arg Tyr Met Asn Glu Gln
 1315 1320 1325
 Lys Asp Asp Glu Val Ala Ile Arg Leu Lys Val Cys Pro Ile Cys Gln
 1330 1335 1340
 Val Pro Ile Arg Lys Asn Leu Ser Tyr Gly Thr Ser Ile Lys Gln Arg
 1345 1350 1355 1360
 Leu Glu Glu Ile Glu Ile Ile Glu Glu Lys Tyr Pro Gly Leu Ile Arg
 1365 1370 1375
 Gly Asn Gly Asn Gln Pro Gly Thr Ala
 1380 1385

<210> 284

<211> 552

<212> PRT

<213> Homo sapiens

<400> 284

Ala Glu Arg Lys Leu Ser Glu Lys Ser Leu Val Val Ala Ala Val Ala
 1 5 10 15
 Pro Asp Asn Arg Asn Pro Ala Phe Thr Thr Met Gly Trp Leu Phe Leu
 20 25 30
 Lys Val Leu Leu Ala Gly Val Ser Phe Ser Gly Phe Leu Tyr Pro Leu
 35 40 45
 Val Asp Phe Cys Ile Ser Gly Lys Thr Arg Gly Gln Lys Pro Asn Phe
 50 55 60
 Val Ile Ile Leu Ala Asp Asp Met Gly Trp Gly Asp Leu Gly Ala Asn

65					70					75				80	
Trp	Ala	Glu	Thr	Lys	Asp	Thr	Ala	Asn	Leu	Asp	Lys	Met	Ala	Ser	Glu
				85					90					95	
Gly	Met	Arg	Phe	Val	Asp	Phe	His	Ala	Ala	Ala	Ser	Thr	Cys	Ser	Pro
			100					105					110		
Ser	Arg	Ala	Ser	Leu	Leu	Thr	Gly	Arg	Leu	Gly	Leu	Arg	Asn	Gly	Val
		115				120						125			
Thr	Arg	Asn	Phe	Ala	Val	Thr	Ser	Val	Gly	Gly	Leu	Pro	Leu	Asn	Glu
	130					135					140				
Thr	Thr	Leu	Ala	Glu	Val	Leu	Gln	Gln	Ala	Gly	Tyr	Val	Thr	Gly	Ile
145				150						155					160
Ile	Gly	Lys	Trp	His	Leu	Gly	His	His	Gly	Ser	Tyr	His	Pro	Asn	Phe
			165					170						175	
Arg	Gly	Phe	Asp	Tyr	Tyr	Phe	Gly	Ile	Pro	Tyr	Ser	His	Asp	Met	Gly
		180						185					190		
Cys	Thr	Asp	Thr	Pro	Gly	Tyr	Asn	His	Pro	Pro	Cys	Pro	Ala	Cys	Pro
		195					200					205			
Gln	Gly	Asp	Gly	Pro	Ser	Arg	Asn	Leu	Gln	Arg	Asp	Cys	Tyr	Thr	Asp
	210					215					220				
Val	Ala	Leu	Pro	Leu	Tyr	Glu	Asn	Leu	Asn	Ile	Val	Glu	Gln	Pro	Val
225					230					235					240
Asn	Leu	Ser	Ser	Leu	Ala	Gln	Lys	Tyr	Ala	Glu	Lys	Ala	Thr	Gln	Phe
			245					250						255	
Ile	Gln	Arg	Ala	Ser	Thr	Ser	Gly	Arg	Pro	Phe	Leu	Leu	Tyr	Val	Ala
		260					265						270		
Leu	Ala	His	Met	His	Val	Pro	Leu	Pro	Val	Thr	Gln	Leu	Pro	Ala	Ala
	275					280					285				
Pro	Arg	Gly	Arg	Lys	Ser	Leu	Tyr	Gly	Ala	Gly	Leu	Trp	Glu	Met	Asp
	290					295					300				
Ser	Leu	Val	Gly	Gln	Ile	Lys	Asp	Lys	Val	Asp	His	Thr	Val	Lys	Glu
305				310						315					320
Asn	Thr	Phe	Leu	Trp	Phe	Thr	Gly	Asp	Asn	Gly	Pro	Trp	Ala	Gln	Lys
		325						330						335	
Cys	Glu	Leu	Ala	Gly	Ser	Val	Gly	Pro	Phe	Thr	Gly	Phe	Trp	Gln	Thr
		340					345					350			
Arg	Gln	Gly	Gly	Ser	Pro	Ala	Lys	Gln	Thr	Thr	Trp	Glu	Gly	Gly	His
	355					360						365			
Arg	Val	Pro	Ala	Leu	Ala	Tyr	Trp	Pro	Gly	Arg	Val	Pro	Val	Asn	Val
	370					375					380				
Thr	Ser	Thr	Ala	Leu	Leu	Ser	Val	Leu	Asp	Ile	Phe	Pro	Thr	Val	Val
385				390						395					400
Ala	Leu	Ala	Gln	Ala	Ser	Leu	Pro	Gln	Gly	Arg	Arg	Phe	Asp	Gly	Val
			405					410						415	
Asp	Val	Ser	Glu	Val	Leu	Phe	Gly	Arg	Ser	Gln	Pro	Gly	His	Arg	Val
		420					425					430			
Leu	Phe	His	Pro	Asn	Ser	Gly	Ala	Ala	Gly	Asp	Phe	Gly	Ala	Leu	Gln
	435					440						445			
Thr	Val	Arg	Leu	Glu	Arg	Tyr	Lys	Ala	Phe	Tyr	Ile	Thr	Gly	Gly	Ala
	450					455					460				
Arg	Ala	Cys	Asp	Gly	Ser	Thr	Gly	Pro	Glu	Leu	Gln	His	Lys	Phe	Pro
465				470						475					480
Leu	Ile	Phe	Asn	Leu	Glu	Asp	Asp	Thr	Ala	Glu	Ala	Val	Pro	Leu	Glu
			485					490						495	
Arg	Gly	Gly	Ala	Glu	Tyr	Gln	Ala	Val	Leu	Pro	Glu	Val	Arg	Lys	Val
		500					505					510			
Leu	Ala	Asp	Val	Leu	Gln	Asp	Ile	Ala	Asn	Asp	Asn	Ile	Ser	Ser	Pro
	515					520						525			
Asp	Tyr	Thr	Gln	Asp	Pro	Ser	Val	Thr	Pro	Cys	Cys	Asn	Pro	Tyr	Gln
	530					535					540				
Ile	Ala	Cys	Arg	Cys	Gln	Ala	Ala								
545					550										

<210> 285
 <211> 294
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(294)
 <223> Xaa = X or * as defined in Table 6

<400> 285
 Pro Val Ala Thr Thr Ile Ser Gln Pro Leu Ser Leu Glu Ala Asp Met
 1 5 10 15
 Trp Ser Ile Gly Val Ile Thr Tyr Ile Leu Leu Ser Gly Ala Ser Pro
 20 25 30
 Phe Leu Gly Asp Thr Lys Gln Glu Thr Leu Ala Asn Ile Thr Ala Val
 35 40 45
 Ser Tyr Asp Phe Asp Glu Glu Phe Phe Ser Glu Thr Ser Glu Leu Ala
 50 55 60
 Gln Asp Phe Ile Arg Lys Leu Leu Gly Xaa Glu Thr Arg Lys Arg Val
 65 70 75 80
 Thr Ile Gln Glu Ala Leu Arg His Pro Trp Ile Thr Ser Lys Gly Glu
 85 90 95
 Gly Arg Ala Pro Glu Gln Arg Lys Thr Glu Pro Thr Gln Leu Lys Thr
 100 105 110
 Lys His Leu Arg Glu Tyr Thr Leu Lys Cys His Ser Ser Met Pro Pro
 115 120 125
 Asn Asn Cys Tyr Val Asn Phe Glu Arg Phe Ala Cys Val Val Glu Asp
 130 135 140
 Val Ala Arg Val Asp Leu Gly Cys Arg Ala Leu Val Glu Ala His Asp
 145 150 155 160
 Thr Ile Gln Asp Asp Val Glu Ala Leu Val Ser Ile Phe Asn Glu Lys
 165 170 175
 Glu Ala Trp Tyr Arg Asp Glu Asn Glu Ser Ala Arg His Asp Leu Ser
 180 185 190
 Gln Leu Arg Tyr Glu Phe Arg Lys Val Glu Ser Leu Lys Lys Leu Leu
 195 200 205
 Arg Glu Asp Ile Gln Ala Thr Gly Cys Ser Leu Gly Ser Met Ala Arg
 210 215 220
 Lys Leu Asp His Leu Gln Ala Gln Phe Glu Ile Leu Arg Gln Glu Leu
 225 230 235 240
 Ser Ala Asp Leu Gln Trp Ile Gln Glu Leu Val Gly Ser Phe Gln Leu
 245 250 255
 Glu Ser Gly Ser Ser Glu Gly Leu Gly Ser Thr Phe Tyr Gln Asp Thr
 260 265 270
 Ser Glu Ser Leu Ser Glu Leu Leu Ser Arg Ser Cys Thr Glu Glu Phe
 275 280 285
 Leu Ala Gly Trp Lys Leu
 290

<210> 286
 <211> 51
 <212> PRT
 <213> Homo sapiens

<400> 286
 Met Val Pro Val Phe Ser Val Glu Lys Asp Gly Glu Glu Leu Gly Ser
 1 5 10 15
 Phe Arg Pro Arg Trp Ala Asp Trp Leu Thr Gly Leu Leu Glu Trp Val
 20 25 30

Ser Val Glu Ser Leu Ser Ile Tyr Cys Ile Ser Gln Pro Val Tyr Met
 35 40 45
 Trp Val Glu
 50

<210> 287
 <211> 6
 <212> PRT
 <213> Homo sapiens

<400> 287
 Met Trp His Leu Ser Val
 1 5

<210> 288
 <211> 116
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(116)
 <223> Xaa = X or * as defined in Table 6

<400> 288
 His Pro His Ser Pro Asp Pro Gly Ser Ala Leu Gly Ser Ser Ser Gly
 1 5 10 15
 Gly Trp Leu Pro Ala Pro Leu Ser Pro Cys Arg Gly Xaa Ala Gly Ala
 20 25 30
 Gly Gly Gly Arg Arg Cys Arg Gly Arg Pro Trp Ser Arg Ala Gly Xaa
 35 40 45
 Ala Cys Ser Gly His Ala Gly Ser Arg Cys Cys Pro Ala Xaa Ser Val
 50 55 60
 Cys Gly Gly Leu Pro Gly Gly Ala Pro Gly Cys Leu Cys Lys Gly Gly
 65 70 75 80
 Ser Ala Gly Phe Cys Cys Gln Gly Pro Gly Cys Ser Cys Ser Gly Cys
 85 90 95
 Ser Gly Ser Gly His Gly Gly Tyr Arg His Arg Gln Gly Arg Pro Leu
 100 105 110
 Ser Ala Ser Gln
 115

<210> 289
 <211> 1654
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(1654)
 <223> Xaa = X or * as defined in Table 6

<400> 289
 Ser Val Tyr Lys Ala Asp Leu Glu Trp Leu Arg Gly Ile Gly Trp Met
 1 5 10 15

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Pro Glu Gly Ser Val Glu Met Asn Arg Val Lys Val Ala Gln Asp Leu
      20      25      30
Val Asn Glu Arg Leu Tyr Arg Thr Arg Pro Glu Ala Leu Ser Phe Thr
      35      40      45
Ser Ile Val Asp Thr Pro Glu Val Val Leu Ala Lys Ala Asn Ser Leu
      50      55      60
Gln Ile Ser Glu Lys Leu Tyr Gln Glu Ala Trp Asn Lys Asp Lys Ser
      65      70      75      80
Asn Ile Thr Ile Pro Ser Asp Thr Pro Glu Met Leu Gln Ala His Ile
      85      90      95
Asn Ala Leu Gln Ile Ser Asn Lys Leu Tyr Gln Lys Asp Trp Asn Asp
      100      105      110
Thr Lys Gln Lys Gly Tyr Asp Ile Arg Ala Asp Ala Ile Glu Ile Lys
      115      120      125
His Ala Lys Ala Ser Arg Glu Ile Ala Ser Glu Tyr Lys Tyr Lys Glu
      130      135      140
Gly Tyr Arg Lys Gln Leu Gly His His Met Gly Phe Arg Thr Leu Gln
      145      150      155      160
Asp Asp Pro Lys Ser Val Trp Ala Ile His Ala Ala Lys Ile Gln Ser
      165      170      175
Asp Arg Glu Tyr Lys Lys Ala Tyr Glu Lys Ser Lys Gly Ile His Asn
      180      185      190
Thr Pro Leu Asp Met Met Ser Ile Val Gln Ala Lys Lys Cys Gln Val
      195      200      205
Leu Val Ser Asp Ile Asp Tyr Arg Asn Tyr Leu His Gln Trp Thr Cys
      210      215      220
Leu Pro Asp Gln Asn Asp Val Ile Gln Ala Lys Lys Ala Tyr Asp Leu
      225      230      235      240
Gln Ser Asp Pro Leu Tyr Arg Asn Ala Trp Glu Lys Glu Lys Ala Asn
      245      250      255
Val Asn Val Pro Ala Asp Thr Pro Leu Met Leu Gln Ser Lys Ile Asn
      260      265      270
Ala Leu Gln Ile Ser Asn Lys Arg Tyr Gln Gln Ala Trp Glu Asp Val
      275      280      285
Lys Met Thr Gly Tyr Asp Leu Arg Ala Asp Ala Ile Gly Ile Gln His
      290      295      300
Ala Lys Ala Ser Arg Asp Ile Ala Ser Asp Tyr Leu Tyr Lys Thr Ala
      305      310      315      320
Tyr Glu Lys Gln Lys Gly His Tyr Ile Gly Cys Arg Ser Ala Lys Glu
      325      330      335
Asp Pro Lys Leu Val Trp Ala Ala Asn Val Leu Lys Met Gln Asn Asp
      340      345      350
Arg Leu Tyr Lys Lys Ala Tyr Asn Asp His Lys Ala Lys Ile Ser Ile
      355      360      365
Pro Val Asp Met Val Ser Ile Ser Ala Ala Lys Glu Gly Gln Ala Leu
      370      375      380
Ala Ser Asp Val Asp Tyr Arg His Tyr Leu His His Trp Ser Cys Phe
      385      390      395      400
Pro Asp Gln Asn Asp Val Ile Gln Ala Arg Lys Ala Tyr Asp Leu Gln
      405      410      415
Ser Asp Thr Glu Pro Cys Ser Leu Ala Gln Ala Gly Val Gln Trp Val
      420      425      430
Ala Asp Met Thr Ala Arg Gly Gln Ser Pro Leu Ala Pro Leu Leu Glu
      435      440      445
Thr Leu Glu Asp Pro Ser Ala Ser His Gly Gly Gln Thr Asp Ala Tyr
      450      455      460
Leu Thr Leu Thr Ser Arg Met Thr Gly Glu Glu Gly Lys Glu Val Ile
      465      470      475      480
Thr Glu Ile Glu Lys Lys Leu Pro Arg Leu Tyr Lys Val Leu Lys Val
      485      490      495
Ser Ser Ile Ile Asp Ser Leu Glu Ile Leu Phe Asn Lys Gly Glu Thr
      500      505      510
His Ser Ala Val Val Asp Phe Glu Ala Leu Asn Val Ile Val Arg Leu
      515      520      525

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Ile	Glu	Gln	Ala	Pro	Ile	Gln	Met	Gly	Glu	Glu	Ala	Val	Arg	Trp	Ala	530	535	540
Lys	Leu	Val	Ile	Pro	Leu	Val	Val	His	Ser	Ala	Gln	Lys	Val	His	Leu	545	550	555
Arg	Gly	Ala	Thr	Ala	Leu	Glu	Met	Gly	Met	Pro	Leu	Leu	Leu	Gln	Lys	565	570	575
Gln	Gln	Glu	Ile	Ala	Ser	Ile	Thr	Glu	Gln	Leu	Met	Thr	Thr	Thr	Leu	580	585	590
His	Arg	Ser	Gly	Ser	Phe	Ile	Asn	Ser	Leu	Leu	Gln	Leu	Glu	Glu	Leu	595	600	605
Gly	Phe	Arg	Ser	Gly	Ala	Pro	Met	Ile	Lys	Lys	Ile	Ala	Phe	Ile	Ala	610	615	620
Trp	Lys	Ser	Leu	Ile	Asp	Asn	Phe	Ala	Leu	Asn	Pro	Asp	Ile	Leu	Cys	625	630	635
Ser	Ala	Lys	Arg	Leu	Lys	Leu	Leu	Met	Gln	Pro	Leu	Ser	Ser	Ile	His	645	650	655
Val	Arg	Thr	Glu	Thr	Leu	Ala	Leu	Thr	Lys	Leu	Glu	Val	Trp	Trp	Tyr	660	665	670
Leu	Leu	Met	Arg	Leu	Gly	Pro	His	Leu	Pro	Ala	Asn	Phe	Glu	Gln	Val	675	680	685
Cys	Val	Pro	Leu	Ile	Gln	Ser	Thr	Ile	Ser	Ile	Asp	Ser	Asn	Ala	Ser	690	695	700
Pro	Gln	Gly	Asn	Ser	Cys	His	Val	Ala	Thr	Ser	Pro	Gly	Leu	Asn	Pro	705	710	715
Met	Thr	Pro	Val	His	Lys	Gly	Ala	Ser	Ser	Pro	Tyr	Gly	Ala	Pro	Gly	725	730	735
Thr	Pro	Arg	Met	Asn	Leu	Ser	Ser	Asn	Leu	Gly	Gly	Met	Ala	Thr	Ile	740	745	750
Pro	Ser	Ile	Gln	Leu	Leu	Gly	Leu	Glu	Met	Leu	Leu	His	Phe	Leu	Leu	755	760	765
Gly	Pro	Glu	Ala	Leu	Ser	Phe	Ala	Lys	Gln	Asn	Lys	Leu	Val	Leu	Ser	770	775	780
Leu	Glu	Pro	Leu	Glu	His	Pro	Leu	Ile	Ser	Ser	Pro	Ser	Phe	Phe	Ser	785	790	795
Lys	His	Ala	Asn	Thr	Leu	Ile	Thr	Ala	Val	His	Asp	Ser	Phe	Val	Ala	805	810	815
Val	Gly	Lys	Asp	Ala	Pro	Gly	Asn	Lys	Lys	Glu	Lys	Pro	Gly	Ser	Glu	820	825	830
Val	Leu	Thr	Leu	Leu	Leu	Lys	Ser	Leu	Glu	Ser	Ile	Val	Lys	Ser	Glu	835	840	845
Val	Phe	Pro	Val	Ser	Lys	Thr	Leu	Gly	Thr	Pro	Ala	Leu	Phe	Leu	Ile	850	855	860
Gln	Leu	Ile	Phe	Asn	Asn	Phe	Leu	Glu	Cys	Gly	Val	Ser	Asp	Glu	Arg	865	870	875
Phe	Phe	Leu	Ser	Leu	Glu	Ser	Leu	Val	Gly	Cys	Val	Leu	Ser	Gly	Pro	885	890	895
Thr	Ser	Pro	Leu	Ala	Phe	Ser	Asp	Ser	Val	Leu	Asn	Val	Ile	Asn	Gln	900	905	910
Asn	Ala	Lys	Gln	Leu	Glu	Asn	Lys	Glu	His	Leu	Trp	Lys	Met	Trp	Ser	915	920	925
Val	Ile	Val	Thr	Pro	Leu	Thr	Glu	Leu	Ile	Asn	Gln	Thr	Asn	Glu	Val	930	935	940
Asn	Gln	Gly	Asp	Ala	Leu	Glu	His	Asn	Phe	Ser	Ala	Ile	Tyr	Gly	Ala	945	950	955
Leu	Thr	Leu	Pro	Val	Asn	His	Ile	Phe	Ser	Glu	Gln	Arg	Phe	Pro	Val	965	970	975
Ala	Thr	Met	Lys	Thr	Leu	Leu	Arg	Thr	Trp	Ser	Glu	Leu	Tyr	Arg	Ala	980	985	990
Phe	Ala	Arg	Cys	Ala	Ala	Leu	Val	Ala	Thr	Ala	Glu	Glu	Asn	Leu	Cys	995	1000	1005
Cys	Glu	Glu	Leu	Ser	Ser	Lys	Ile	Met	Ser	Ser	Ser	Glu	Asp	Glu	Gly	1010	1015	1020
Phe	Ser	Asn	Leu	Leu	Phe	Val	Asp	Arg	Ile	Ile	Tyr	Ile	Ile	Thr	Val	1025	1030	1035
																		1040

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Met Val Asp Cys Ile Asp Phe Ser Pro Tyr Asn Ile Lys Tyr Gln Pro
      1045      1050      1055
Lys Val Lys Ser Pro Gln Arg Pro Ser Asp Trp Ser Lys Lys Lys Asn
      1060      1065      1070
Glu Pro Leu Gly Lys Leu Thr Ser Leu Phe Lys Leu Ile Val Lys Val
      1075      1080      1085
Ile Tyr Ser Phe His Thr Leu Ser Phe Lys Glu Ala His Ser Asp Thr
      1090      1095      1100
Leu Phe Thr Ile Gly Asn Ser Ile Thr Gly Ile Ile Ser Ser Val Leu
1105      1110      1115      1120
Gly His Ile Ser Leu Pro Ser Met Ile Arg Lys Ile Phe Ala Thr Leu
      1125      1130      1135
Thr Arg Pro Leu Ala Leu Phe Tyr Glu Asn Ser Lys Leu Asp Glu Val
      1140      1145      1150
Pro Lys Val Tyr Ser Cys Leu Asn Asn Lys Leu Glu Lys Leu Leu Gly
      1155      1160      1165
Glu Ile Ile Ala Cys Leu Gln Phe Ser Tyr Thr Gly Thr Tyr Asp Ser
      1170      1175      1180
Glu Leu Leu Glu Gln Leu Ser Pro Leu Leu Cys Ile Ile Phe Leu His
1185      1190      1195      1200
Lys Asn Lys Gln Ile Arg Lys Gln Ser Ala Gln Phe Trp Asn Ala Thr
      1205      1210      1215
Phe Ala Lys Val Met Met Leu Val Tyr Pro Glu Glu Leu Lys Pro Val
      1220      1225      1230
Leu Thr Gln Ala Lys Gln Lys Phe Leu Leu Leu Leu Pro Gly Leu Glu
      1235      1240      1245
Thr Val Glu Met Met Glu Glu Ser Ser Gly Pro Tyr Ser Asp Gly Leu
      1250      1255      1260
Lys Leu Glu Ser Ser Ser Leu Lys Val Lys Gly Glu Ile Leu Leu Glu
1265      1270      1275      1280
Glu Glu Lys Ser Thr Asp Phe Val Phe Ile Pro Pro Glu Gly Lys Asp
      1285      1290      1295
Ala Lys Glu Arg Ile Leu Thr Asp His Gln Lys Glu Val Leu Lys Thr
      1300      1305      1310
Lys Arg Phe Glu Glu Gln Met Asp Ser Asp Ile Val Ile Pro Gln Asp
      1315      1320      1325
Val Thr Glu Asp Cys Gly Met Ala Glu His Leu Glu Lys Ser Ser Leu
      1330      1335      1340
Ser Asn Asn Glu Cys Gly Ser Leu Asp Lys Thr Ser Pro Glu Met Ser
1345      1350      1355      1360
Asn Ser Asn Asn Asp Glu Arg Lys Lys Ala Leu Ile Ser Ser Arg Lys
      1365      1370      1375
Thr Ser Thr Glu Cys Ala Ser Ser Thr Glu Asn Ser Phe Val Val Ser
      1380      1385      1390
Ser Ser Ser Val Ser Asn Thr Thr Val Ala Gly Thr Pro Pro Tyr Pro
      1395      1400      1405
Thr Ser Arg Arg Gln Thr Phe Ile Thr Leu Glu Lys Phe Asp Gly Ser
      1410      1415      1420
Glu Asn Arg Pro Phe Ser Pro Ser Pro Leu Asn Asn Ile Ser Ser Thr
1425      1430      1435      1440
Val Thr Val Lys Asn Asn Gln Glu Thr Met Ile Lys Thr Asp Phe Leu
      1445      1450      1455
Pro Lys Ala Lys Gln Arg Glu Gly Thr Phe Ser Lys Ser Asp Ser Glu
      1460      1465      1470
Lys Ile Val Asn Gly Thr Lys Arg Ser Ser Arg Arg Ala Gly Lys Ala
      1475      1480      1485
Glu Gln Thr Gly Asn Lys Arg Ser Lys Pro Leu Met Arg Ser Glu Pro
      1490      1495      1500
Glu Lys Asn Thr Glu Glu Ser Val Glu Gly Ile Val Val Leu Glu Asn
1505      1510      1515      1520
Asn Pro Pro Gly Leu Asn Gln Thr Glu Cys Val Ser Asp Asn Gln
      1525      1530      1535
Val His Leu Ser Glu Ser Thr Met Glu His Asp Asn Thr Lys Leu Lys
      1540      1545      1550

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Ala Ala Thr Val Glu Asn Ala Val Leu Leu Glu Thr Asn Thr Val Glu
 1555 1560 1565
 Glu Lys Asn Val Glu Ile Asn Leu Glu Ser Lys Glu Asn Thr Pro Pro
 1570 1575 1580
 Val Val Ile Ser Ala Asp Gln Met Val Asn Glu Asp Ser Gln Val Gln
 1585 1590 1595 1600
 Ile Thr Pro Asn Gln Lys Thr Leu Arg Arg Ser Ser Arg Arg Arg Tyr
 1605 1610 1615
 Arg Ser Ser Arg Val Tyr His Xaa Lys Pro Arg Xaa Gly Lys Xaa Ser
 1620 1625 1630
 Ser Lys Lys Gly Thr Thr Xaa Gly Arg Arg Lys Thr Ser Ser Glu Glu
 1635 1640 1645
 Ser Ile Ala Tyr Lys Arg
 1650

<210> 290
 <211> 108
 <212> PRT
 <213> Homo sapiens

<400> 290
 Lys Asp Ala Tyr Met Phe Lys Lys Gly Leu Leu Ala Leu Ala Leu Val
 1 5 10 15
 Phe Ser Met Pro Val Phe Ala Ala Glu His Trp Ile Asp Val Arg Val
 20 25 30
 Pro Glu Gln Tyr Gln Gln Glu His Val Gln Gly Ala Ile Asn Ile Pro
 35 40 45
 Leu Lys Glu Val Lys Glu Arg Ile Ala Thr Ala Val Pro Asp Lys Asn
 50 55 60
 Asp Thr Val Lys Val Tyr Cys Asn Ala Gly Arg Gln Ser Gly Gln Ala
 65 70 75 80
 Lys Glu Ile Leu Ser Glu Met Gly Tyr Thr His Val Glu Asn Ala Gly
 85 90 95
 Gly Leu Lys Asp Ile Ala Met Pro Lys Val Lys Gly
 100 105

<210> 291
 <211> 119
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(119)
 <223> Xaa = X or * as defined in Table 6

<400> 291
 Ser Ser Pro Ser Cys His Leu Val Lys Lys Ile Lys Ile Lys Met Lys
 1 5 10 15
 Ser Pro Ala Leu Arg Gly Leu Ser Arg Gln His Thr Lys Ser Pro Val
 20 25 30
 Thr Phe Trp Trp Met Thr Phe Gly Asp Thr Ser Arg Pro Ser Gln Asp
 35 40 45
 Thr Leu Pro Met Asp Leu Gln Leu Leu Gly Val Thr Lys Val Cys
 50 55 60
 Ser Lys Ala Thr Ser Pro Thr Ser Gln Arg Gly Gln Glu Val Ile Ser
 65 70 75 80
 Thr Pro Thr Ser Lys Ser Gly Pro Phe Ile Gly Arg Gly Ser Xaa Gly

				85					90				95				
Xaa	Ser	Gly	Arg	Trp	Glu	Arg	Pro	Ser	Cys	Cys	Leu	His	Phe	Ser	Tyr		
			100					105					110				
Pro	Gln	Leu	Arg	Gly	Leu	Cys											
			115														

<210> 292

<211> 354

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(354)

<223> Xaa = X or * as defined in Table 6

<400> 292

Arg	Glu	Pro	Ala	Gly	Ala	Gly	Ala	Tyr	Met	Arg	Ala	Cys	Ala	Arg	Val		
1				5					10					15			
Arg	Arg	Arg	Gly	Asp	Arg	Arg	Pro	Arg	Arg	Ser	Pro	Arg	Pro	Arg	Asp		
			20					25					30				
Pro	Ala	Val	Arg	Ala	Arg	Ala	Arg	Ser	Ala	Pro	Pro	Pro	Leu	Phe	Ile		
		35					40					45					
Ala	Ala	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Trp	Arg	Leu	Tyr	Ala	Asp	Ser		
	50					55					60						
Gly	Glu	Glu	Tyr	Gly	Ile	Met	Ala	Phe	Ala	Leu	Phe	Val	Leu	Leu	Gly		
	65				70					75					80		
Phe	Ala	Leu	Leu	Gly	Thr	His	Gly	Ala	Ser	Gly	Ala	Ala	Gly	Thr	Val		
				85					90					95			
Phe	Thr	Thr	Val	Glu	Asp	Leu	Gly	Ser	Lys	Ile	Leu	Leu	Thr	Cys	Ser		
			100					105					110				
Leu	Asn	Asp	Ser	Ala	Thr	Glu	Val	Thr	Gly	His	Arg	Trp	Leu	Lys	Gly		
	115					120						125					
Gly	Val	Val	Leu	Lys	Glu	Asp	Ala	Leu	Pro	Gly	Gln	Lys	Thr	Glu	Ser		
	130					135					140						
Phe	Lys	Val	Asp	Ser	Asp	Asp	His	Val	Gly	Met	Lys	Tyr	Ser	Cys	Val		
	145				150					155				160			
Phe	Leu	Pro	Glu	Pro	His	Gly	His	Gly	Pro	Thr	Ile	Gln	Ala	Ser	Thr		
			165					170						175			
Gly	Pro	Pro	Arg	Val	Glu	Gly	Leu	Xaa	Ser	Ser	Phe	Arg	Thr	His	Ser		
			180					185					190				
Thr	Arg	Gly	Lys	Thr	Gly	Leu	Val	Gly	Ser	Cys	Lys	Ser	Glu	Phe	Val		
	195					200						205					
Pro	Pro	Val	Thr	Asp	Trp	Ala	Pro	Trp	Tyr	Lys	Ile	Thr	Asp	Ser	Glu		
	210					215						220					
Pro	Gln	Gly	Pro	Ser	Leu	Asn	Ala	Gln	Arg	Thr	Arg	Phe	Phe	Val	Gly		
	225				230					235				240			
Pro	Ser	Ala	Gly	Pro	Val	Lys	Ser	Tyr	Gln	His	Xaa	Glu	Pro	Glu	His		
		245						250					255				
Ile	Gly	Pro	Pro	Pro	Ala	Arg	Asn	Arg	Cys	Asn	Gly	Thr	Ser	Ser	Lys		
		260						265					270				
Gly	Leu	Arg	Pro	Arg	Pro	Leu	Gln	Phe	Leu	Arg	Val	Arg	Thr	Ala	Thr		
	275					280						285					
Xaa	Ala	Ala	Leu	Trp	Pro	Phe	Leu	Gly	Ile	Val	Gly	Glu	Val	Leu	Val		
	290					295					300						
Leu	Val	Thr	Ile	Ile	Phe	Ile	Tyr	Glu	Lys	Arg	Arg	Lys	Pro	Glu	Asp		
	305				310					315				320			
Val	Leu	Asp	Asp	Asp	Ala	Gly	Ser	Ala	Pro	Leu	Lys	Glu	Ser	Ala			
		325						330					335				
Gly	Gln	His	Gln	Asn	Asp	Lys	Gly	Lys	Lys	Arg	Ser	Ala	Arg	Gly	Asn		
		340						345					350				

Phe Ser

<210> 293
 <211> 312
 <212> PRT
 <213> Homo sapiens

<400> 293
 Met Lys Val Leu Leu Glu Ser Val Lys Glu Arg Ala Glu Glu Glu Lys
 1 5 10 15
 Leu Ala Ala Ala His Leu Arg Ser Phe Ala Ala Lys Lys Ala Lys Lys
 20 25 30
 Tyr Asp Ser Val Lys Lys Glu Lys Thr Leu Gln Asp Val Asp Leu Thr
 35 40 45
 Gln His Gln His Lys Gln Thr Arg Ala Leu Ser Gly Gly Leu Lys Arg
 50 55 60
 Lys Leu Ser Leu Gly Ile Ala Phe Met Gly Met Ser Arg Thr Val Val
 65 70 75 80
 Leu Asp Glu Pro Thr Ser Gly Val Asp Pro Cys Ser Arg His Ser Leu
 85 90 95
 Trp Asp Ile Leu Leu Lys Tyr Arg Glu Gly Arg Thr Ile Ile Phe Thr
 100 105 110
 Thr His His Leu Asp Glu Ala Glu Ala Leu Ser Asp Arg Val Ala Val
 115 120 125
 Leu Gln His Gly Arg Leu Arg Cys Cys Gly Pro Pro Phe Cys Leu Lys
 130 135 140
 Glu Ala Tyr Gly Gln Gly Leu Arg Leu Thr Leu Thr Arg Gln Pro Ser
 145 150 155 160
 Val Leu Glu Ala His Asp Leu Lys Asp Met Ala Cys Val Thr Ser Leu
 165 170 175
 Ile Lys Ile Tyr Ile Pro Gln Ala Phe Leu Lys Asp Ser Ser Gly Ser
 180 185 190
 Glu Leu Thr Tyr Thr Ile Pro Lys Asp Thr Asp Lys Ala Cys Leu Lys
 195 200 205
 Gly Leu Phe Gln Ala Leu Asp Glu Asn Leu His Gln Leu His Leu Thr
 210 215 220
 Gly Tyr Gly Ile Ser Asp Thr Thr Leu Glu Glu Ala Glu Gly Arg Thr
 225 230 235 240
 Ala Ala Pro Glu Pro Pro Met Leu Glu Asp Gly His Ala Val Thr Gln
 245 250 255
 Arg Phe Ser Phe Ile Gln Val Val Gly Cys Glu Asp Asp Arg Thr Thr
 260 265 270
 Trp Val Gln Ala Gln Gly Ala Ser Ala Pro Gly Gly Gln Arg Pro Gln
 275 280 285
 Glu Asp Leu Pro Ser Phe Pro Gln Asp Gly Arg Ser Arg Ala Gln Phe
 290 295 300
 Lys Asp Pro His Gln Phe Ser Asn
 305 310

<210> 294
 <211> 581
 <212> PRT
 <213> Homo sapiens

<400> 294
 Met Ala Ser His Ala Tyr Asp Lys Asn Gln Asn Ala Asn Val Leu Val
 1 5 10 15

His Leu Cys Phe Tyr Asn Arg Ile Pro Lys Thr Gly Ala Tyr Tyr Leu
 20 25 30
 Asp Ser Arg Ser Val Ser Ile Ser Tyr Leu Ile Gly His His Ile Asp
 35 40 45
 Met Gly Leu Glu Thr Ala Thr Ser Lys Asn Glu Phe Ile Phe Asp Ser
 50 55 60
 Ala Ser Thr Leu Leu Gly Met Leu Phe Arg Lys Pro Ser Gln His Ser
 65 70 75 80
 Leu Ser Leu Phe Ser Lys Lys Phe Gln Glu Asn Leu Ile Tyr Leu Glu
 85 90 95
 Ser Asp Asp Cys Leu Pro Pro Pro Pro Pro Pro Trp Ser Glu Pro
 100 105 110
 Pro Ser Phe Leu Thr Trp Thr Ile Val Thr Val Phe Gln Trp Val Ser
 115 120 125
 Leu Leu Leu Ser Leu Pro Asn Ile Gln Val Ile Leu Tyr Arg Ala Val
 130 135 140
 Gly Val Val Pro Ser Gln Pro Lys Ser Asp Asn Leu Lys Gly Trp Gly
 145 150 155 160
 Ser Gly Arg Val Val Lys Glu Lys Leu Arg Ser Glu Ile Pro Asp Trp
 165 170 175
 Lys Ile Lys Ser Ile His Ile Leu Glu Arg Thr Ala Ser Ser Ser Thr
 180 185 190
 Glu Pro Ser Val Ser Arg Gln Leu Leu Glu Pro Glu Pro Val Pro Leu
 195 200 205
 Ser Lys Glu Ala Asp Ser Trp Glu Ile Ile Glu Gly Leu Lys Ile Gly
 210 215 220
 Gln Thr Asn Val Gln Lys Pro Asp Lys His Glu Gly Phe Met Leu Lys
 225 230 235 240
 Lys Arg Lys Trp Pro Leu Lys Gly Trp His Lys Ile Gln Lys Gly Lys
 245 250 255
 Val His Gly Ser Ile Asp Val Gly Leu Ser Val Met Ser Ile Lys Lys
 260 265 270
 Lys Ala Arg Arg Ile Asp Leu Asp Thr Glu Glu His Ile Tyr His Leu
 275 280 285
 Lys Val Lys Ser Val Phe Asn Ser Phe Ser Ala Ile Ile Arg Gly Asn
 290 295 300
 Asp Leu Pro Thr Pro Val Val Lys Ser Gln Asp Trp Phe Asp Ala Trp
 305 310 315 320
 Val Ser Lys Leu Arg His His Arg Leu Tyr Arg Gln Asn Glu Ile Val
 325 330 335
 Arg Ser Pro Arg Asp Ala Ser Phe His Ile Phe Pro Ser Thr Ser Thr
 340 345 350
 Ala Glu Ser Ser Pro Ala Ala Asn Val Ser Val Met Asp Gly Lys Met
 355 360 365
 Gln Pro Asn Ser Phe Pro Trp Gln Ser Pro Leu Pro Cys Ser Asn Ser
 370 375 380
 Leu Pro Ala Thr Cys Thr Thr Gly Gln Ser Lys Val Ala Ala Trp Leu
 385 390 395 400
 Gln Asp Ser Glu Glu Met Asp Arg Cys Ala Glu Asp Leu Ala His Cys
 405 410 415
 Gln Ser Asn Leu Val Glu Leu Ser Lys Leu Leu Gln Asn Leu Glu Ile
 420 425 430
 Leu Gln Arg Thr Gln Ser Ala Pro Asn Phe Thr Asp Met Gln Ala Asn
 435 440 445
 Cys Val Asp Ile Ser Lys Lys Asp Lys Arg Val Thr Arg Arg Trp Arg
 450 455 460
 Thr Lys Ser Val Ser Lys Asp Thr Lys Ile Gln Leu Gln Val Pro Phe
 465 470 475 480
 Ser Ala Thr Met Ser Pro Val Arg Leu His Ser Ser Asn Pro Asn Leu
 485 490 495
 Cys Ala Asp Ile Glu Phe Gln Thr Pro Pro Ser His Leu Thr Asp Pro
 500 505 510
 Leu Glu Ser Ser Thr Asp Tyr Thr Lys Leu Gln Glu Glu Phe Cys Leu
 515 520 525

Ile Ala Gln Lys Gly Lys Gly Ala Ser Lys Lys Gln Ala Lys Arg Asn
 530 535 540
 Ala Ala Glu Lys Phe Leu Ala Lys Phe Ser Asn Ile Ser Pro Glu Asn
 545 550 555 560
 His Ile Ser Leu Val Ser Asn Val Asp Ser Tyr Asp Val Asn Val Ile
 565 570 575
 Lys His Phe Leu Gln
 580

<210> 295
 <211> 416
 <212> PRT
 <213> Homo sapiens

<400> 295
 Met Leu Arg Thr Arg Lys Ala Pro His Ser Trp Val Lys Ser Ser Ser
 1 5 10 15
 Asn Thr Val His Tyr Arg Val Ser Val Val Cys Leu His Asp His Val
 20 25 30
 Thr Asp Trp Glu Trp Gln Leu Thr Ala Thr Ala Arg His Pro Lys Arg
 35 40 45
 Val Ser His Tyr Ile Leu Trp Asp Gln Glu Lys Thr Lys Ile Lys Ile
 50 55 60
 Arg Lys Asp Ile Ile Arg Ile Leu Pro Ser Leu Asp Val Glu Val Lys
 65 70 75 80
 Asp Ile Thr Asp Ser Tyr Asp Ala Asn Trp Phe Leu Gln Leu Leu Ser
 85 90 95
 Thr Glu Asp Leu Phe Glu Met Thr Ser Lys Glu Phe Pro Ile Val Thr
 100 105 110
 Glu Val Ile Glu Ala Pro Glu Gly Asn His Leu Pro Gln Ser Ile Leu
 115 120 125
 Gln Pro Gly Lys Thr Ile Val Ile His Lys Lys Tyr Gln Ala Ser Arg
 130 135 140
 Ile Leu Ala Ser Glu Ile Arg Ser Asn Phe Pro Lys Arg His Phe Leu
 145 150 155 160
 Ile Pro Thr Ser Tyr Lys Gly Lys Phe Lys Arg Arg Pro Arg Glu Phe
 165 170 175
 Pro Thr Ala Tyr Asp Leu Glu Ile Ala Lys Ser Glu Lys Glu Pro Leu
 180 185 190
 His Val Val Ala Thr Lys Ala Phe His Ser Pro His Asp Lys Leu Ser
 195 200 205
 Ser Val Ser Val Gly Asp Gln Phe Leu Val His Gln Ser Glu Thr Thr
 210 215 220
 Glu Val Leu Cys Glu Gly Ile Lys Lys Val Val Asn Val Leu Ala Cys
 225 230 235 240
 Glu Lys Ile Leu Lys Lys Ser Tyr Glu Ala Ala Leu Leu Pro Leu Tyr
 245 250 255
 Met Glu Gly Gly Phe Val Glu Val Ile His Asp Lys Lys Gln Tyr Pro
 260 265 270
 Ile Ser Glu Leu Cys Lys Gln Phe Arg Leu Pro Phe Asn Val Lys Val
 275 280 285
 Ser Val Arg Asp Leu Ser Ile Glu Glu Asp Val Leu Ala Ala Thr Pro
 290 295 300
 Gly Leu Gln Leu Glu Glu Asp Ile Thr Asp Ser Tyr Leu Leu Ile Ser
 305 310 315 320
 Asp Phe Ala Asn Pro Thr Glu Cys Trp Glu Ile Pro Val Gly Arg Leu
 325 330 335
 Asn Met Thr Val Gln Leu Val Ser Asn Phe Ser Arg Asp Ala Glu Pro
 340 345 350
 Phe Leu Val Arg Thr Leu Val Glu Glu Ile Thr Glu Glu Gln Tyr Tyr
 355 360 365

```

Met Met Arg Arg Tyr Glu Ser Ser Ala Ser His Pro Pro Pro Arg Pro
 370          375          380
Pro Lys His Pro Ser Val Glu Glu Thr Lys Leu Thr Leu Leu Thr Leu
385          390          395          400
Ala Glu Glu Arg Thr Val Asp Leu Pro Lys Ser Pro Lys Arg Arg Arg
      405          410          415

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<210> 296
<211> 302
<212> PRT
<213> Homo sapiens

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<400> 296
Met Phe Ala Phe Glu Pro Leu Gly Gly Cys Arg Pro Trp Arg Leu Ser
 1          5          10          15
Leu Pro Gly Leu Gly Ser Arg Leu Phe Arg Thr Tyr Gly Ala Ala Asp
      20          25          30
Gly Arg Arg Gln Arg Arg Pro Gly Arg Glu Ala Ala Gln Trp Phe Pro
      35          40          45
Pro Gln Asp Arg Arg Arg Phe Phe Asn Ser Ser Gly Ser Ser Asp Ala
      50          55          60
Arg Met Gly Asp Pro Ser Gln Ser Asp Asp Pro Asp Asp Pro Asp Asp
      65          70          75          80
Pro Asp Phe Pro Gly Ser Pro Val Arg Arg Arg Arg Cys Pro Gly
      85          90          95
Gly Arg Val Pro Lys Asp Arg Pro Ser Leu Thr Val Thr Pro Lys Arg
      100          105          110
Trp Lys Leu Arg Ala Arg Pro Ser Leu Thr Val Thr Pro Arg Arg Leu
      115          120          125
Gly Leu Arg Ala Arg Pro Pro Gln Lys Cys Ser Thr Pro Cys Gly Pro
      130          135          140
Leu Arg Leu Pro Pro Phe Pro Ser Arg Asp Ser Gly Arg Leu Ser Pro
      145          150          155          160
Asp Leu Ser Val Cys Gly Gln Pro Arg Asp Gly Asp Glu Leu Gly Ile
      165          170          175
Ser Ala Ser Leu Phe Ser Ser Leu Ala Ser Pro Cys Pro Gly Ser Pro
      180          185          190
Thr Pro Arg Asp Ser Val Ile Ser Ile Gly Thr Ser Ala Cys Leu Val
      195          200          205
Ala Ala Ser Ala Val Pro Ser Gly Leu His Leu Pro Glu Val Ser Leu
      210          215          220
Asp Arg Ala Ser Leu Pro Cys Ser Gln Glu Glu Ala Thr Gly Gly Ala
      225          230          235          240
Lys Asp Thr Arg Met Gly Ser Val Arg Val Leu Arg Asp Pro Val Gly
      245          250          255
Val Asn Leu Tyr Glu His Ser Val Ser Lys Cys His Val Gly Gln Pro
      260          265          270
Asp Thr Asp Pro Arg Glu Lys Val Lys Ala Ala Pro Glu Glu Leu Cys
      275          280          285
Leu His Ala Leu Gln His Pro Arg Ser Glu Gln Ala Asp Cys
      290          295          300

```

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<210> 297
<211> 98
<212> PRT
<213> Homo sapiens

```

<400> 297

Gln Gly Ala Phe Trp Leu Leu Phe Ser Ser Pro Arg Ser Phe Phe Leu
 1 5 10 15
 Leu Ser Val Pro Trp Trp Leu Pro Glu Ser Ser Arg Trp Leu Leu Leu
 20 25 30
 His Gly Lys Ser Gln Leu Ala Val Gln Asn Leu Gln Lys Val Ala His
 35 40 45
 Arg Gly Asp Trp Pro Gly Ser Gly His Pro Ala Pro Gln Ser Gln His
 50 55 60
 Ser Ser Leu Arg Arg Ser Ala Ala Arg Ser Arg Pro Pro Cys Trp Ala
 65 70 75 80
 Arg Arg Trp Arg Ala Pro Pro His Thr Pro Arg Val Ala Gly Gly Ser
 85 90 95
 Gly Cys

<210> 298

<211> 175

<212> PRT

<213> Homo sapiens

<400> 298

Glu Ser Val Thr Phe Glu Asp Val Ala Val Glu Phe Ile Gln Glu Trp
 1 5 10 15
 Ala Leu Leu Asp Ser Ala Arg Arg Ser Leu Cys Lys Tyr Arg Met Leu
 20 25 30
 Asp Gln Cys Arg Thr Leu Ala Ser Arg Gly Thr Pro Pro Cys Lys Pro
 35 40 45
 Ser Cys Val Ser Gln Leu Gly Gln Arg Ala Glu Pro Lys Ala Thr Glu
 50 55 60
 Arg Gly Ile Leu Arg Ala Thr Cys Val Ala Trp Glu Ser Gln Leu Lys
 65 70 75 80
 Pro Glu Glu Leu Pro Ser Met Gln Asp Leu Leu Glu Glu Ala Ser Ser
 85 90 95
 Arg Asp Met Gln Met Gly Pro Gly Leu Phe Leu Arg Met Gln Leu Val
 100 105 110
 Pro Ser Ile Glu Glu Arg Glu Thr Pro Leu Thr Arg Glu Asp Arg Pro
 115 120 125
 Ala Leu Gln Asp Pro Pro Trp Ser Leu Gly Cys Thr Gly Leu Lys Ala
 130 135 140
 Ala Met Gln Ile Gln Arg Val Val Ile Pro Val Pro Thr Leu Gly His
 145 150 155 160
 Arg Asn Pro Trp Val Ala Arg Asp Ser Gly Ala Ile Gly Asn Gly
 165 170 175

<210> 299

<211> 197

<212> PRT

<213> Homo sapiens

<400> 299

Pro Leu Pro Leu Asp Gln Arg Leu Leu Ala Ser Ile Thr Pro Ser Pro
 1 5 10 15
 Ser Gly Gln Ser Ile Ile Arg Thr Gln Pro Gly Ala Gly Val His Pro
 20 25 30
 Lys Ala Asp Gly Ala Leu Lys Gly Glu Ala Glu Gln Ser Ala Gly His
 35 40 45

```

Pro Ser Glu His Leu Phe Ile Cys Glu Glu Cys Gly Arg Cys Lys Cys
  50          55          60
Val Pro Cys Thr Ala Ala Arg Pro Leu Pro Ser Cys Trp Leu Cys Asn
  65          70          75          80
Gln Arg Cys Leu Cys Ser Ala Glu Ser Leu Leu Asp Tyr Gly Thr Cys
          85          90          95
Leu Cys Cys Val Lys Gly Leu Phe Tyr His Cys Ser Thr Asp Asp Glu
          100          105          110
Asp Asn Cys Ala Asp Glu Pro Cys Ser Cys Gly Pro Ser Ser Cys Phe
          115          120          125
Val Arg Trp Ala Ala Met Ser Leu Ile Ser Leu Phe Leu Pro Cys Leu
          130          135          140
Cys Cys Tyr Leu Pro Thr Arg Gly Cys Leu His Leu Cys Gln Gln Gly
          145          150          155          160
Tyr Asp Ser Leu Arg Arg Pro Gly Cys Arg Cys Lys Arg His Thr Asn
          165          170          175
Thr Val Cys Arg Lys Ile Ser Ser Gly Ser Ala Pro Phe Pro Lys Ala
          180          185          190
Gln Glu Lys Ser Val
          195

```

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<210> 300
<211> 523
<212> PRT
<213> Homo sapiens

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<400> 300
Met Lys Thr Cys Leu Ala Phe Pro Leu Ala Phe His His Asp Ser Asn
  1          5          10          15
Gly Ser Ala Val Leu Arg Leu Gln Ala Thr His Gly Ile Ser Ser Asp
          20          25          30
Ser Pro Leu Pro Ser Val Glu Lys Ala Ser His Ser Pro Asp Pro Ser
          35          40          45
Glu Tyr Phe Arg Lys His Pro Pro Val Arg Arg Ser Gly Leu Arg Thr
          50          55          60
Lys Arg Thr Ser Pro Gly Pro Gly Ala Arg Val Pro Gly Ser Gln Ser
          65          70          75          80
Phe Arg Ser Ala Glu Ala Cys Gly Val Ala Ala Leu Glu Cys Trp Arg
          85          90          95
Arg Arg Val Pro Val Pro Leu Ser Ser Pro Ala Glu Val Gln Val Leu
          100          105          110
Leu Lys Lys Ala Leu Arg Pro Glu Ser Arg Pro Phe Arg Asn Gln Ile
          115          120          125
Leu His Asn Cys Glu Arg Asn Trp Gly Asn Lys Gly Trp Lys Gly Leu
          130          135          140
Val Gly Arg Ser Glu Ser Gln Thr Gly Gln Ser Glu Lys Leu Ser Met
          145          150          155          160
Ser Ser His His Arg Gly Thr Val Arg Glu Glu Leu Val Val Glu Glu
          165          170          175
Tyr Ile Gly Gly Trp Cys Leu Cys Gly Ser Ala Trp Lys Leu Leu Val
          180          185          190
Thr Gly Leu Glu Gln Leu Leu Phe Ser Arg Thr Arg Pro Gln Glu Glu
          195          200          205
Ala Val Asp Lys Thr Trp Arg Thr Ala Arg Gln Leu Glu Ser Gly Thr
          210          215          220
Leu Leu Cys Arg His Cys Ile Thr Leu Pro Trp Pro Ser Glu Arg Asn
          225          230          235          240
Gly Gly Cys Phe Leu Ser Pro Ser Asn Met Leu Val Cys Glu Leu Arg
          245          250          255
Val Leu Ser Val Ile Val Ala Ser Pro Glu Pro Ser Thr Glu His Thr
          260          265          270

```

Gln Glu His Leu Ser Gly Asp Glu Phe Glu Lys Ser Gln Pro Ser Arg
 275 280 285
 Lys Glu Lys Ser Leu Gly Leu Leu Cys His Lys Phe Leu Ala Arg Tyr
 290 295 300
 Pro Asn Tyr Pro Asn Pro Ala Val Asn Asn Asp Ile Cys Leu Asp Glu
 305 310 315 320
 Val Ala Glu Glu Leu Asn Val Glu Arg Arg Arg Ile Tyr Asp Ile Val
 325 330 335
 Asn Val Leu Glu Ser Leu His Met Val Ser Arg Leu Ala Lys Asn Arg
 340 345 350
 Tyr Thr Trp His Gly Arg His Asn Leu Asn Lys Thr Leu Gly Thr Leu
 355 360 365
 Lys Ser Ile Gly Glu Glu Asn Lys Tyr Ala Glu Gln Ile Met Met Ile
 370 375 380
 Lys Lys Lys Glu Tyr Glu Gln Glu Phe Asp Phe Ile Lys Ser Tyr Thr
 385 390 395 400
 Ser Val Asn Ser Arg Lys Asp Lys Ser Leu Arg Val Met Ser Gln Lys
 405 410 415
 Phe Val Met Leu Phe Leu Val Ser Thr Pro Gln Ile Val Ser Leu Glu
 420 425 430
 Val Ala Ala Lys Ile Leu Ile Gly Glu Asp His Val Glu Asp Leu Asp
 435 440 445
 Lys Ser Lys Phe Lys Thr Gly Ser Leu Val Arg Leu Phe Ala Pro Cys
 450 455 460
 Leu Ser Gly Ala Gly Ser Lys Leu Pro Gly Leu Val Glu Ala Leu Ala
 465 470 475 480
 Phe Glu Val Ser Leu Ala Ala Phe Ser Val Val Ala Ser Val Glu Ser
 485 490 495
 Phe Glu Pro Val Ala Leu Glu Glu Trp Val Val His Thr Val Gly Leu
 500 505 510
 Arg Pro Trp Gly Gly Val Thr Leu Trp Trp Ala
 515 520

<210> 301
 <211> 81
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(81)
 <223> Xaa = X or * as defined in Table 6

<400> 301
 Met Asp Leu Ile Val Tyr His Lys Lys Ser Asp Ile Ser Asn Gln Pro
 1 5 10 15
 Ser Ile Pro Thr Cys Ala Leu Phe Phe Pro Cys Val Ser Leu Glu Pro
 20 25 30
 Phe Gln Leu Phe Pro Val Lys Gln Thr Ala Arg Arg Pro Pro Tyr
 35 40 45
 Ser Ser Pro Gly Lys Ser Thr Gly Asn Val Ile Pro Phe Gly His Gly
 50 55 60
 Phe Pro Thr Leu Gln Pro Lys Xaa Gln Ile Thr Pro Val Gly Gly Gln
 65 70 75 80
 Tyr

<210> 302
 <211> 585

<212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(585)
 <223> Xaa = X or * as defined in Table 6

<400> 302
 Met Arg Gln Thr Lys Thr Glu Tyr Ile Gln Glu Phe Asn Gln Glu Ala
 1 5 10 15
 Thr Val Ala Arg Ala Leu Glu Gly Gln Glu Lys Pro Thr Glu Gly Pro
 20 25 30
 Arg Asn Thr Cys Leu Gly Ser Asn Asn Met Tyr Asp Ile Phe Asn Leu
 35 40 45
 Asn Asp Lys Ala Leu Cys Phe Thr Lys Cys Arg Gln Ser Gly Ser Asp
 50 55 60
 Ser Cys Asn Val Glu Asn Leu Gln Arg Tyr Trp Leu Asn Tyr Glu Ala
 65 70 75 80
 His Leu Met Lys Glu Gly Leu Thr Gln Lys Val Asn Thr Pro Phe Leu
 85 90 95
 Lys Ala Leu Val Gln Asn Leu Ser Thr Asn Thr Ala Glu Asp Phe Tyr
 100 105 110
 Phe Ser Leu Glu Pro Ser Gln Val Pro Arg Gln Val Met Lys Asp Glu
 115 120 125
 Asp Lys Pro Pro Asp Arg Val Arg Leu Pro Lys Ser Leu Phe Arg Ser
 130 135 140
 Leu Pro Gly Asn Arg Ser Val Val Arg Leu Ala Val Thr Ile Leu Asp
 145 150 155 160
 Ile Gly Pro Gly Thr Leu Phe Lys Gly Pro Arg Leu Gly Leu Gly Asp
 165 170 175
 Gly Ser Gly Val Leu Asn Asn Arg Leu Val Gly Leu Ser Val Gly Gln
 180 185 190
 Met His Val Thr Lys Leu Ala Glu Pro Leu Glu Ile Val Phe Ser His
 195 200 205
 Gln Arg Pro Pro Pro Asn Met Thr Leu Thr Cys Val Phe Trp Asp Val
 210 215 220
 Thr Lys Ala Leu Val Gly Gly Tyr Asp Ile Leu Ala Ile Tyr Glu Val
 225 230 235 240
 Glu His Phe Gln Gln Glu Gln Cys Val Ala Val Ile Ser Val Cys Ser
 245 250 255
 Arg Gly Gly Lys Gly Ser Ala Glu Cys Gly His Trp Gly Lys Gly Leu
 260 265 270
 Thr Thr Glu His Ser Ser Pro Val Pro Ala Val Thr His Leu Ser Leu
 275 280 285
 Ala Arg Ile Ala Glu Lys Gly Lys Ala Gly Cys Pro Ala Arg Ala Cys
 290 295 300
 Arg Val His Ser Trp Val Leu Val Leu Ser Gly Lys Arg Glu Val Pro
 305 310 315 320
 Glu Asn Phe Phe Ile Asp Pro Phe Thr Gly His Ser Tyr Ser Thr Gln
 325 330 335
 Asp Glu His Phe Leu Gly Ile Glu Ser Leu Trp Asn His Lys Asn Tyr
 340 345 350
 Trp Ile Asn Met Gln Asp Cys Trp Asn Cys Cys Lys Val Pro Arg Glu
 355 360 365
 Gly Glu Leu Gly Asp Pro Glu Glu Arg Leu Ala His Leu Ser Trp Trp
 370 375 380
 Leu Gly Leu Ser Val His Leu His Gly Gly Arg Ser Gln Ser Ala Ala
 385 390 395 400
 Pro Glu Leu Pro Ser His His Pro Val Pro Ala Ala Leu Met Val Tyr
 405 410 415
 Glu Pro Leu Pro Ala Thr Thr Gly Leu Asp Leu Xaa Pro Gly Xaa Pro
 420 425 430

Cys Glu Met Gly Val His Ala Pro Gly Asp Xaa Xaa Val Ser Ala Val
 435 440 445
 Leu Asp Xaa Arg Arg Arg Gln Trp Asp Lys Arg Xaa Gly Xaa Cys Gly
 450 455 460
 Lys Ser Gly Gln Gly Gly Xaa Gly Xaa Glu Leu Arg His Ala Pro Leu
 465 470 475 480
 Val Val Glu Gln Ile Glu Ile Ser Pro Glu Gly Thr Asn Ile Leu Glu
 485 490 495
 Ile Lys Glu Trp Tyr Gln Asn Arg Glu Asp Met Leu Glu Leu Lys His
 500 505 510
 Ile Asn Lys Thr Thr Asp Leu Lys Thr Asp Tyr Phe Lys Pro Gly His
 515 520 525
 Pro Gln Ala Leu Arg Val His Ser Tyr Lys Ser Met Gln Pro Glu Met
 530 535 540
 Asp Arg Val Ile Glu Phe Tyr Glu Thr Ala Arg Val Asp Gly Leu Met
 545 550 555 560
 Lys Arg Glu Glu Thr Pro Arg Thr Met Thr Glu Tyr Tyr Gln Gly Arg
 565 570 575
 Pro Asp Phe Leu Ser Tyr Arg His Ala
 580 585

<210> 303

<211> 457

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(457)

<223> Xaa = X or * as defined in Table 6

<400> 303

Gly Asp Gln Lys Val His Pro Phe Ser Thr Pro Ser Pro Gly Thr Pro
 1 5 10 15
 Ala Phe His Ile Pro Thr Thr Phe Ser Pro Ala Ala Gly Pro Gly His
 20 25 30
 His Leu Pro Met Asp Pro Gly Glu Gly Leu Ala Glu Gly Pro Gly Leu
 35 40 45
 Pro Gly Ser Ser Gly Xaa Arg Pro Leu Xaa Val Pro Ser Arg Arg Ala
 50 55 60
 Ser His Cys Pro Pro Gly Ala Thr Lys Ala Arg Gly Gly Arg Cys Arg
 65 70 75 80
 Gly Pro Ala Ala Thr Thr Gly Xaa Ala Ala Cys Ala Gly Arg Thr Ala
 85 90 95
 Ala Pro Gly Xaa Pro Gly Ala Ser Pro Pro Ala Ala Gln Ala Leu His
 100 105 110
 His Ser Leu Gln Glu Pro Gly Glu His Arg Gly Arg Pro Gly Pro Ser
 115 120 125
 Ala Ser Ala Pro Ser Ala Gly Thr Val Asp Gln Val Gly Gly Gly Ala
 130 135 140
 Glu Arg Met Pro Thr Thr Pro Gly Pro Arg His Ala Val Gly Glu Cys
 145 150 155 160
 Gly Pro Thr Cys Ser Ala Ser Leu Arg Gly Pro Leu Xaa Pro Leu Pro
 165 170 175
 Asn Leu Ala Ala Pro Ala Gln Trp Gly Ser His Gln Leu Gln Gly Glu
 180 185 190
 Glu Gln Ile Gln Val Pro Ser Cys Phe Ala Pro Gly Ile Gln Arg
 195 200 205
 Leu Leu Pro Arg Pro Gln Thr Gln Glu Pro Gly Phe Xaa Thr Gln Thr
 210 215 220
 Pro Asp Pro Gly Leu Lys Pro Gln Asp Ser Lys Pro Arg Leu Pro Gly

```

225          230          235          240
Leu Gln Thr Gln Thr Pro Asp Pro Gly Pro Arg Thr Arg Ala Asp Gly
          245          250          255
Phe Pro Asp Gln Arg Gly Pro Val Gly Gln Gly Gln Trp Glu Gly Ala
          260          265          270
Pro Gly Gly His Thr Leu Gly Asn Ser Gly Gly Ser Cys Leu Ala Gly
          275          280          285
Pro Pro Trp Xaa Arg Ser Glu Gly His Glu Glu Cys Pro Ser Ser Cys
          290          295          300
Gln Ser Gln Phe Gly Glu Leu Arg Leu Trp Leu Pro Arg Gly Gly Trp
305          310          315
Ala Glu Gly Val Ser Ala Gly Ser His Gly Pro Pro Trp Pro Ala Gly
          325          330          335
Pro Ala Pro Pro Gly Pro Gln Pro Leu Gly Trp Asp Ala Gly Pro His
          340          345          350
Phe Pro Glu Glu Ser Arg Thr Arg Pro Gly Pro Asp Pro Glu Pro Xaa
          355          360          365
Lys Asp His Gly Thr Val Leu Xaa Leu Thr Gln Arg Lys His Arg Asp
          370          375          380
Gly His Lys Glu Pro Arg Thr Lys Ile Gln Leu Pro Val Pro Gly Ala
385          390          395
Glu Gly Gln Thr Cys Pro Pro Glu Pro Trp Ala Gly Ala His Arg Arg
          405          410          415
Asn Ala Asn Trp Gln Ala Gln Gly Ser Arg Arg Glu Arg Pro Ser Gly
          420          425          430
Phe Gln Thr Pro Arg Ser His Trp Val Pro Ser Ala Gly Arg Ser Gly
          435          440          445
Phe Leu Gly Pro Gln Phe Ser Cys Leu
          450          455

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<210> 304
<211> 42
<212> PRT
<213> Homo sapiens

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```

<400> 304
Met Ser Gly Arg Val Phe Arg Cys Gln Ala Leu Val Ala Tyr Thr Val
 1          5          10          15
Leu Ser Glu Leu Phe Thr Glu Ala Lys Glu Gln Arg Leu Ala Thr Asp
          20          25          30
Glu Gly Gln Lys Glu Phe Ser Ala Glu Ser
          35          40

```

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<210> 305
<211> 41
<212> PRT
<213> Homo sapiens

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```

<400> 305
Met Ser Gly Arg Val Phe Arg Cys Gln Ala Leu Val Ala Tyr Thr Val
 1          5          10          15
Leu Ser Glu Leu Phe Thr Glu Ala Lys Glu Gln Arg Leu Ala Thr Asp
          20          25          30
Glu Gly Gln Lys Glu Phe Ser Ala Glu
          35          40

```

<210> 306
 <211> 827
 <212> PRT
 <213> Homo sapiens

<400> 306
 Gly Lys Tyr Tyr Lys Leu Ser Ser Gly Thr Ala Pro Thr Cys Val Ser
 1 5 10 15
 Leu Gly Trp Gly Leu Ala Arg Gly Asp Ser Ala Ala Pro Ala Leu Gly
 20 25 30
 Ser Arg Thr Ser Ala Cys Ala Pro Cys Ser His Gly Thr Trp Lys Leu
 35 40 45
 Ser Leu Glu Pro Ser Asp Arg Leu Ser Pro Cys Asp Arg Ser Ser Glu
 50 55 60
 Glu Ala His Thr His Ala Pro His Arg Leu Leu Ala Leu Val Ala Ser
 65 70 75 80
 Leu Pro Trp Ser Arg Leu Pro Leu Leu Ala Pro Gln Ser His Ser Glu
 85 90 95
 Ala Glu Ala Thr Ser Gln Pro Thr Gly Val Glu Asn His His Gln Lys
 100 105 110
 Thr Arg Tyr Val Lys Ala Gly Gly Pro Val Ile Cys Arg Ser Leu Pro
 115 120 125
 Glu Ser Arg Gly Phe Leu Trp Ala Ser Glu Gly Arg Lys Cys Met Leu
 130 135 140
 Ile Gly Ser Trp Ala Ala Met Gly Arg Leu Arg Lys Ser Thr Ile Ser
 145 150 155 160
 Ser Arg Phe Gly Pro Gln Thr Leu Ala Gly Thr Gly Arg Pro Gln Ala
 165 170 175
 Ile Pro Val Leu Lys Lys His Ser Asp Ala Val Leu Leu Gly Val Cys
 180 185 190
 Phe Leu Lys Leu Leu His Gln His His Gln Glu Leu Gly Glu Asn Ala
 195 200 205
 Asp Ser Gln Thr Leu Pro Gln Thr His Trp Glu Phe Ile Leu Ser Glu
 210 215 220
 Asp Tyr Asn Lys Met Thr Pro Val Lys Asn Tyr Gln Val Leu Glu Val
 225 230 235 240
 Leu Ala Arg Ala Met Arg Gln Glu Lys Gln Ile Lys Ser Ile Gln Leu
 245 250 255
 Gly Lys Glu Glu Val Lys Leu Ser Val Phe Ala Asp Asp Met Ile Val
 260 265 270
 Tyr Leu Glu Asn Pro Ile Val Ser Ala Gln Asn Leu Leu Lys Leu Ile
 275 280 285
 Ser Asn Phe Ser Lys Val Ser Gly Tyr Lys Ile Asn Val Gln Lys Ser
 290 295 300
 Gln Ala Phe Leu Tyr Thr Asn Asn Arg Gln Thr Glu Ser Gln Ile Ile
 305 310 315 320
 Ser Glu Leu Pro Phe Thr Ile Pro Ser Lys Arg Ile Lys Tyr Leu Gly
 325 330 335
 Ile Gln Leu Thr Arg Asp Val Lys Asp Leu Phe Lys Glu Asn Tyr Lys
 340 345 350
 Pro Leu Leu Asn Glu Ile Lys Glu Asp Thr Asn Lys Trp Lys Asn Ile
 355 360 365
 Pro Cys Ser Trp Val Gly Arg Ile Asn Ile Met Lys Met Ala Ile Leu
 370 375 380
 Pro Arg Val Ile Tyr Ile Phe Asn Ala Ile Ser Ile Lys Leu Pro Met
 385 390 395 400
 Thr Phe Phe Thr Glu Leu Glu Lys Thr Thr Leu Lys Phe Ile Trp Asn
 405 410 415
 Gln Lys Arg Ala Arg Ile Ala Lys Thr Ile Leu Ser Gln Lys Asn Lys
 420 425 430
 Ala Gly Gly Ile Thr Leu Pro Asp Phe Lys Leu Tyr Tyr Lys Ala Thr
 435 440 445
 Val Thr Lys Thr Ala Trp Tyr Trp Tyr Gln Asn Arg Gly Val Asp Gln

```

      450              455              460
Trp Asn Arg Ile Glu Pro Ser Glu Ile Ile Pro His Ile His Asn His
465              470              475              480
Leu Ile Phe Asp Lys Pro Asp Lys Asn Lys Lys Trp Gly Lys Asp Ser
      485              490              495
Leu Phe Thr Lys Trp Cys Trp Glu Asn Trp Leu Ala Ile Cys Arg Lys
      500              505              510
Leu Lys Leu Asp Pro Phe Leu Thr Pro Tyr Thr Lys Ile Asn Ser Thr
      515              520              525
Trp Ile Lys Asp Leu Asn Val Arg Pro Lys Thr Ile Lys Thr Leu Glu
      530              535              540
Glu Asn Leu Gly Ile Thr Ile Gln Asp Ile Gly Met Gly Lys Asp Phe
545              550              555              560
Met Ser Lys Thr Pro Lys Ala Met Ala Thr Lys Ala Lys Ile Asp Lys
      565              570              575
Trp Asp Leu Ile Lys Leu Lys Ser Phe Cys Thr Ala Lys Glu Thr Thr
      580              585              590
Ile Arg Val Asn Arg Gln Pro Thr Glu Trp Glu Lys Ile Phe Thr Ile
      595              600              605
Tyr Pro Ser Asp Lys Gly Leu Ile Pro Arg Ile Tyr Lys Glu Leu Lys
      610              615              620
Gln Asn Leu Gln Glu Lys Ile Lys Gln Pro His Gln Lys Val Gly Lys
625              630              635              640
Gly Tyr Lys Gln Thr Phe Leu Lys Arg Arg His Leu Cys Ser Gln Gln
      645              650              655
Thr His Glu Lys Met Phe Ile Ile Thr Gly His Gln Arg Asn Ala Lys
      660              665              670
Gln Asn His Asn Lys Ile His Leu Thr Pro Val Arg Met Ala Ile Ile
      675              680              685
Lys Lys Ser Gly Asn Asn Arg Asp Met Asp Glu Ala Gly Asn His His
      690              695              700
Ser Glu Gln Thr Ile Ala Arg Thr Glu Asn Gln Ala Pro Tyr Leu Leu
705              710              715              720
Thr His Arg Trp Glu Leu Asn Asn Glu Asn Thr Trp Thr Gln Val Glu
      725              730              735
Glu His His Thr Leu Gly Pro Ile Val Gly Val Ile Cys Arg Lys Val
      740              745              750
Phe Pro Gly Asn Ser Gly Pro Ser Lys Pro Ser Gly Leu His Phe Ser
      755              760              765
Gln Pro Leu Pro Gln Val Thr Ser Val Val Ala Lys Ile Thr Ile Val
      770              775              780
Pro Trp Glu Met Lys Leu Ile Ala Met Gly Val Gln Asp Glu Leu Asn
785              790              795              800
Ile Ala Phe His Lys Asn His Leu Leu Met Asn Asp Thr Thr Ile His
      805              810              815
Met Thr Pro Tyr Ile Gln Pro Ala Pro Lys Ser
      820              825

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<210> 307

<211> 135

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(135)

<223> Xaa = X or * as defined in Table 6

<400> 307

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Thr Pro Leu Pro Val Cys His Phe Thr Cys Arg Lys Asn His Leu Lys
  1              5              10              15

```

Gly Met Glu Asn Leu Cys Leu His Lys Lys Cys Met Trp Met Ser Thr
 20 25 30
 Val Ala Phe Ser Ile Ile Ala Lys Thr Trp Lys Gln Pro Arg Cys Pro
 35 40 45
 Ser Ala Ala Pro Ser Trp Lys Gln Pro Thr His Leu Thr Thr Gly Asp
 50 55 60
 Trp Ala Asn Gly Leu Gly Xaa Phe Ser Thr Arg Glu Tyr Val Thr Ala
 65 70 75 80
 Xaa Glu Arg Thr Asn Gln Ser Lys Pro Asp Thr Thr Thr Trp Val Asn
 85 90 95
 Leu Thr Asp Val Gln Leu Ser Asn Ser Ser Gln Ala Pro Arg Gly Val
 100 105 110
 Ser Thr Thr Leu Gln Phe Pro Val Leu Gly Thr Val Asp Lys Ser Gly
 115 120 125
 Val Thr Met Thr Phe Trp Val
 130 135

<210> 308
 <211> 313
 <212> PRT
 <213> Homo sapiens

<400> 308
 Met Gly Asn Lys Thr Tyr Gly Gly Gln Asn Gln Met Leu Ile Phe Ala
 1 5 10 15
 Phe Thr Leu His Ser Leu Phe Leu Asn Ser Gly Asp Gly Arg Leu Ser
 20 25 30
 Phe Glu Ser Ser Ser Gln Lys Pro Gly Gly Phe Arg Asn Ile Ala Ile
 35 40 45
 Gln Thr Ser Pro Ser Leu Arg Lys His Phe Pro Val Phe Lys Arg Lys
 50 55 60
 Arg Leu Thr Ala Ser Lys Ser Val Glu Glu Met Pro Thr Ala Ser Gln
 65 70 75 80
 Ser Ala Ile His Val Asn Gly Asn Leu Ser Glu Gln Asp Ile Val Ser
 85 90 95
 Ser Asp Leu Ala Tyr Leu Arg Leu Ala Gln His Leu Glu Asp Gly Pro
 100 105 110
 Arg Arg Val Lys Val Ser His Ala Phe Leu Pro Arg Val Pro Lys Val
 115 120 125
 Gln Ser Asn Gly Pro Val Ser Ile Cys Leu Glu Ala Gly Thr Trp Arg
 130 135 140
 Ser Leu Glu Lys Ala Thr Ala Ala Ile Gln Val Pro Asp Asp Ile Tyr
 145 150 155 160
 His Ser Pro Ser Trp Glu Ala Arg Glu Ser Ala Leu Ser Pro Asp Arg
 165 170 175
 Ser Ala Glu His Asn Ser Leu Ser Arg Pro Ser Asp Pro Gly Leu Ser
 180 185 190
 Leu Gln Pro Gln Leu Leu Pro Thr Leu Cys Leu Pro Phe His Val Leu
 195 200 205
 Tyr Thr Arg Ser Pro Gln Ser Leu Gly His Gly Pro Ile Ala Val His
 210 215 220
 Gly Leu Leu Gly Thr Met Leu Arg Ser Arg Arg Thr Trp Ser Phe Leu
 225 230 235 240
 Tyr Pro Gly Phe Leu Pro Trp Cys Ser Gly Arg Ile Gly Ser Arg Val
 245 250 255
 Gly Leu Glu Asn Glu Cys Lys Val Ser Leu Ser Gly Ser Ser Ser Gln
 260 265 270
 Pro Met Gly Glu Pro Glu Gly Arg Trp Ser Ser Pro Glu Val Gly Pro
 275 280 285
 Leu Ala Ser Pro Gly Ser Pro Leu Ile Ala Trp Ala Lys Leu Arg Phe
 290 295 300

Val Pro Pro Val Asp Asp Leu Pro Val
305 310

<210> 309
<211> 509
<212> PRT
<213> Homo sapiens

<400> 309
Met Asp Ser Gln Glu Val Glu Lys Tyr Pro Asn Thr Ser Val Ala Cys
1 5 10 15
Glu Glu Ile Pro Phe Ser Gly Ile His Val Ala Gly Gly Lys Ser Gly
20 25 30
Ala Leu Glu His Gly Lys Asp Asp Leu Asp Glu Pro Ile Glu Asn Pro
35 40 45
Leu Phe Cys Phe Ser Ser Phe Ser Asn Ala Leu Ala Ile Leu Leu Pro
50 55 60
Lys Val Phe Leu Lys Asn Ile His Ile Leu Gln Phe Ile Tyr Arg Ser
65 70 75 80
Phe His Leu Leu Thr Met Ala Lys Ala Lys Phe Glu Gly Ala Glu Ser
85 90 95
Val Glu Pro Val Ser Pro Ser Gln Pro Lys Arg Pro Ser Tyr Val Pro
100 105 110
Leu Glu Glu Leu Trp Thr Arg Leu Thr Lys Gly Asn Ser Arg Pro Gln
115 120 125
Gln Arg Asp Arg Glu Lys Gly Gly Trp Met Lys Gly Val Gln Gln Gly
130 135 140
His Gln Gly Val Gly Lys Gln Glu Glu Gly Ser Glu Asn Ile Lys Glu
145 150 155 160
Lys Ala Gly Ile Val Val Cys Glu Val Pro Asn Asn Lys Leu Asp Lys
165 170 175
Phe Met Gly Ile Leu Ser Trp Lys Asp Ser Lys His Ser Leu Asn Asn
180 185 190
Glu Lys Ile Ile Leu Arg Gly Cys Ile Leu Arg Asn Thr Ser Trp Cys
195 200 205
Phe Gly Met Val Ile Phe Ala Gly Pro Asp Thr Lys Leu Met Gln Asn
210 215 220
Ser Gly Lys Thr Lys Phe Lys Arg Thr Ser Ile Asp Arg Leu Met Asn
225 230 235 240
Thr Leu Val Leu Trp Ile Met Leu Ile Ser Gln Pro Val Val Glu Phe
245 250 255
Ile Met Arg Gly His Ser Tyr Phe Ile Asn Trp Asp Arg Lys Met Tyr
260 265 270
Tyr Ser Arg Lys Ala Ile Pro Ala Val Ala Arg Thr Thr Leu Asn
275 280 285
Glu Glu Leu Gly Gln Ile Glu Tyr Ile Phe Ser Asp Lys Thr Gly Thr
290 295 300
Leu Thr Gln Asn Ile Met Thr Phe Lys Arg Cys Ser Ile Asn Gly Arg
305 310 315 320
Ile Tyr Gly Glu Val His Asp Asp Leu Asp Gln Lys Thr Glu Ile Thr
325 330 335
Gln Leu Ile His Arg Trp Leu Ala Arg Leu Lys Lys Lys Lys Arg Glu
340 345 350
Lys Asn Gln Thr Asp Thr Ile Lys Asn Asp Lys Gly Asn Ile Thr Thr
355 360 365
Asp Leu Ala Glu Thr Gln Thr Thr Ile Arg Glu Tyr Tyr Lys His Leu
370 375 380
Tyr Thr Asn Lys Leu Glu Asn Leu Glu Glu Met Asp Lys Phe Leu Asp
385 390 395 400
Ala Tyr Thr Leu Ser Arg Leu Asn Gln Glu Glu Val Glu Ser Leu Ser
405 410 415

```

Arg Pro Ile Thr Ser Ser Glu Ile Glu Ala Val Ile Asn Ser Leu Pro
      420                      425                      430
Thr Lys Lys Ser Pro Gly Pro Asp Arg Phe Thr Ala Glu Leu Tyr Gln
      435                      440                      445
Lys Tyr Lys Glu Glu Leu Glu Lys Glu Pro Val Asp Phe Ser Val Lys
      450                      455                      460
Ser Gln Ala Asp Arg Glu Phe Gln Phe Phe Asp His Asn Leu Met Glu
465                      470                      475                      480
Ser Ile Lys Met Gly Asp Pro Lys Val His Glu Phe Leu Arg Leu Leu
      485                      490                      495
Ala Leu Cys His Thr Val Met Ser Glu Glu Asn Ser Ala
      500                      505

```

<210> 310

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(70)

<223> Xaa = X or * as defined in Table 6

<400> 310

```

Asp Trp Thr Val Gly Phe Val Gly Asn Ser Asp Thr Glu Leu Pro Gly
 1          5          10          15
Ser Val Gly Arg Arg Ser Leu Trp Glu Ser Ser Tyr Ser Thr Arg Thr
      20          25          30
Arg Asn Gln Gly Arg Gln Ala Ile Gln Ile Gln His Ser Xaa Leu Arg
      35          40          45
Glu Val Glu Arg Lys Ser Gly Gln Lys Ala Thr Met Ser Ser Gly Gly
 50          55          60
Gly Tyr Cys Gln Pro Glu
65          70

```

<210> 311

<211> 250

<212> PRT

<213> Homo sapiens

<400> 311

```

Ala Ile Arg Gln Glu Lys Glu Ile Lys Gly Ile Gln Leu Gly Lys Glu
 1          5          10          15
Glu Val Lys Leu Ser Leu Phe Ala Asp Asp Met Ile Leu Tyr Leu Glu
      20          25          30
Asn Pro Ile Val Ser Ala Gln Asn Leu Leu Lys Leu Ile Ser Asn Phe
      35          40          45
Ser Lys Val Ser Gly Tyr Lys Ile Asn Val Gln Lys Ser Gln Ala Phe
 50          55          60
Leu Tyr Thr Asn Asn Arg Gln Thr Glu Ser Gln Ile Met Ser Glu Leu
65          70          75          80
Pro Phe Thr Ile Ala Ser Lys Arg Ile Lys Tyr Leu Gly Ile Gln Leu
      85          90          95
Thr Arg Asp Val Lys Asp Leu Phe Lys Glu Asn Tyr Lys Leu Leu Leu
      100          105          110
Lys Glu Ile Lys Glu Asp Arg Asn Lys Trp Lys Asn Ile Pro Cys Ser
      115          120          125
Trp Val Gly Arg Ile Asn Met Val Lys Met Ala Ile Leu Pro Lys Val

```

```

      130              135              140
Ile Tyr Gly Phe Asn Ala Ile Pro Ile Lys Leu Pro Met Ile Phe Phe
145              150              155              160
Thr Glu Leu Glu Lys Thr Thr Ser Lys Phe Ile Trp Asn Gln Lys Arg
      165              170              175
Ala His Ile Ala Lys Ser Ile Leu Ser Gln Lys Asn Lys Ala Gly Gly
      180              185              190
Ile Thr Pro Pro Asp Phe Lys Leu Tyr Tyr Lys Ala Thr Val Thr Lys
      195              200              205
Thr Ala Trp Thr Arg Lys Ile Tyr Ser Ala Lys Lys Arg Lys Val Lys
      210              215              220
Ile Ser Val Glu Pro Val Tyr Ser Gly Val Thr Leu Thr Thr Ala Ile
225              230              235              240
Gln Leu Val Pro Leu Leu Cys Thr Ala Leu
      245              250

```

```

<210> 312
<211> 297
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(297)
<223> Xaa = X or * as defined in Table 6

```

```

      <400> 312
Met Asp Tyr Glu Lys Ala Asp Lys Arg Pro Thr Pro Trp Glu Ala Ala
  1              5              10              15
Ala Lys Ser Pro Leu Gly Leu Val Asp Asp Ala Phe Gln Pro Lys Asn
      20              25              30
Ile Gln Glu Ser Ile Val Ala Asn Val Val Ser Ala Ala Arg Arg Lys
      35              40              45
Val Leu Pro Gly Pro Pro Glu Asp Trp Asn Glu Arg Leu Ser Tyr Ile
      50              55              60
Pro Gln Thr Gln Lys Ala Tyr Met Gly Ser Cys Gly Arg Gln Glu Tyr
      65              70              75              80
Asn Val Thr Ala Asn Asn Met Ser Thr Thr Ser Gln Tyr Gly Ser
      85              90              95
Gln Leu Pro Tyr Ala Tyr Tyr Arg Gln Ala Ser Arg Asn Asp Ser Ala
      100              105              110
Ile Met Ser Met Glu Thr Arg His Leu Tyr Thr Arg Gln Leu Tyr Cys
      115              120              125
Tyr Ser Phe Gly Asp Ser Gly Asn Phe Cys Glu Asn Thr Asn Gly Arg
      130              135              140
Pro Ala Ala Asp Ala Val Arg Gly Leu Thr Ile Leu Ser Leu Ser Thr
145              150              155              160
Thr Ser Ile Pro Ser Ser Gly Ile Ser Glu Ala Leu Ile Ser Glu Asn
      165              170              175
Glu Asn Lys Asn Leu Glu His Leu Thr His Gly Gly Tyr Val Glu Ser
      180              185              190
Thr Thr Leu Gln Ile Arg Pro Ala Thr Lys Thr Gln Cys Thr Glu Phe
      195              200              205
Phe Leu Ala Pro Val Lys Thr Glu Val Pro Leu Ala Glu Asn Gln Arg
      210              215              220
Ser Gly Pro Asp Cys Ala Gly Ser Leu Lys Glu Glu Thr Gly Pro Ser
225              230              235              240
Tyr Gln Arg Ala Pro Gln Met Pro Asp Ser Gln Arg Gly Arg Val Ala
      245              250              255
Glu Glu Leu Ile Leu Arg Glu Lys Val Glu Ala Ser Thr Gln Asn Asn
      260              265              270

```


Tyr Tyr Val Gly Glu Leu Thr Gly Val Thr Leu Gln Asn Gly Tyr Gly
 275 280 285
 Glu Lys Pro Ile Leu Ala Thr Gln Xaa
 290 295

<210> 313
 <211> 325
 <212> PRT
 <213> Homo sapiens

<400> 313
 Met Leu Lys Tyr Thr Gly Ala His Gln Glu Val Glu Leu Ser Ala Pro
 1 5 10 15
 Ile Val Thr Lys Met Ala Thr Gln Tyr Leu Arg Glu Asn Leu Phe Gly
 20 25 30
 Arg Phe Asp Asn Asp Asn Phe Cys Leu Leu Asn Gly Asp Ala Val Ile
 35 40 45
 Phe Arg Met Tyr Val Ser Trp Lys Leu Val Glu Lys Glu Arg Thr Glu
 50 55 60
 Ile Met Leu Lys Tyr Thr Gly Ala His Gln Glu Thr Trp Leu Lys Asp
 65 70 75 80
 Leu Glu Glu Ser Pro Leu Tyr Glu Ala Leu Ser Met Arg Gly Gln Asp
 85 90 95
 Lys Glu Thr Leu Gly Leu Trp Ile Gln Leu Pro Trp Cys Pro Trp Gly
 100 105 110
 Lys Ala Val Gln Met His Met Asn Pro Ser Ser Phe Gln Leu Asp Thr
 115 120 125
 Lys Pro Gly Lys Gly Glu Leu Ala Gly Arg Leu Ile Ile Pro His Gln
 130 135 140
 Glu Ala Ser Ile Leu Glu Leu Ser Leu Leu Leu Met Thr Cys Cys Val
 145 150 155 160
 Glu Arg Glu Gly Lys Thr Ser Val Arg Val Ala Ala Val Gly Glu Cys
 165 170 175
 Thr Ala Ser Glu Thr Pro Asn Gln Gly Ala Gly Arg Leu Ser Leu Trp
 180 185 190
 Gln Gln Leu Thr Ser Lys Lys Glu Thr Ile Met Glu Lys Glu His Thr
 195 200 205
 Asp Cys Val Ser Gln Thr Val Ala Leu Ile Ser Thr Cys Val Lys Glu
 210 215 220
 Gly Gly Ser Arg Pro Ala Asp Lys Asp Leu Glu Glu Gly Gly Gly Leu
 225 230 235 240
 Glu Ala Glu Ser Pro Lys Gln Ser Pro Asn Leu Cys Val Ile Leu Arg
 245 250 255
 His Asn Leu Ala Ser Arg Pro Gly Gln Leu Ala Leu Val Thr Val Gly
 260 265 270
 Thr Met Gln Gly Arg Pro Leu Ser His Ser Ser Glu Val Lys Gly Thr
 275 280 285
 Thr Phe Val Thr His Ser Val Pro Ala Gly Lys Glu Lys Asp Glu Glu
 290 295 300
 Arg Gly Ile Gly Asp Leu Glu His Ala Arg Asp Leu Arg Asn Ser Pro
 305 310 315 320
 Thr Pro Leu Phe Tyr
 325

<210> 314
 <211> 301
 <212> PRT
 <213> Homo sapiens

```

<400> 314
Met Ser Glu Leu Pro Phe Thr Ile Ala Ser Lys Arg Ile Lys Tyr Leu
 1          5          10          15
Gly Ile Gln Leu Thr Arg Asp Val Lys Asp Phe Phe Lys Glu Asn Tyr
          20          25          30
Lys Pro Leu Leu Asn Glu Ile Lys Glu Glu Thr Asn Lys Trp Lys Asn
          35          40          45
Ile Pro Cys Ser Trp Val Gly Arg Ile Asn Ile Val Lys Met Ala Ile
 50          55          60
Leu Pro Gln Arg Leu Pro His Gly Phe Leu Pro Asn Met Lys Leu Glu
 65          70          75          80
Val Val Asp Lys Arg Asn Pro Arg Leu Ile Arg Val Ala Thr Ile Val
          85          90          95
Asp Val Asp Asp Gln Arg Val Lys His Ser Met Thr Ala Ser Ser Gly
          100          105          110
Ser Gly Val Ser Ala Asp Leu Asn Thr Ala Ser Gln Pro Leu Trp Leu
          115          120          125
Leu Lys Thr Ala Leu Ala Val Ser Ser Ser Val Lys Val His Pro Pro
          130          135          140
Val Ser Gly Leu Ile Phe Ser Ser Ser Arg Thr Leu Leu Ser Phe Met
          145          150          155          160
Gly Ile Met Arg Glu Asp Leu Gly Phe Ser Arg Arg Gln Ile Leu His
          165          170          175
Phe Pro Met Ala Leu Ser Lys Ser Ala Gly Arg Arg Ser Lys Ile Gly
          180          185          190
Gln Leu Asp Ala Leu Ser Gln Asp Phe Gly Leu Arg Asp Arg Asp Ser
          195          200          205
Ser Lys Lys Gly Thr Gly Tyr Pro Asn Pro Glu Asn Phe Ser Trp Thr
          210          215          220
Glu Tyr Leu Glu Ala Thr Gln Thr Asn Ala Val Pro Ala Lys Val Phe
          225          230          235          240
Lys Met Asp Ser Asp Val Gly Glu Asn Arg Lys Ile Leu Arg Asp Glu
          245          250          255
Arg Pro Asn Tyr Ser Gln Tyr Thr Pro Phe Ser Arg Cys Asp Asn Ala
          260          265          270
Ser Tyr Lys Glu Asn Val Phe Leu Gln Lys Leu Glu Arg Asn Thr Pro
          275          280          285
Asp Ile Ala Glu Arg Phe Asp Cys Leu Leu Leu Thr Tyr
          290          295          300

```

<210> 315

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(80)

<223> Xaa = X or * as defined in Table 6

```

<400> 315
Met Met Ser Trp Ser Ser Ala Glu Lys Gly Pro Glu Gly His Arg Arg
 1          5          10          15
Arg Glu Trp Pro Ser Gln Trp Glu Asp Glu Pro Xaa Asn Gln Asn Gly
          20          25          30
Glu Ser Arg Lys Lys Glu Arg Lys Glu Lys Arg Arg Lys Glu Thr Xaa
          35          40          45
Glu Glu Arg Arg Gly Glu Lys Arg Glu Lys Arg Glu Lys Lys Arg Arg
          50          55          60
Arg Glu Gly Arg Met Ser Ile Ser Phe Ala Arg Arg Tyr Ser Ile Leu

```

65

70

75

80

<210> 316
 <211> 106
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(106)
 <223> Xaa = X or * as defined in Table 6

<400> 316
 Ser Gln Arg Thr Ala Gly Asn Pro Cys Leu His Pro Val Ser Leu Cys
 1 5 10 15
 Gly Ser Ala Ser Trp Met Pro Met Ile Met Pro Gln Arg Trp Ser Ser
 20 25 30
 Leu Cys Ser Ala Met Glu Lys Pro Ala Ser Pro Cys Leu Xaa Met Pro
 35 40 45
 Pro Gln Ala Thr Cys Trp Cys Pro Ser Arg Leu Pro Met Ala Trp Ala
 50 55 60
 Ser Gly His Xaa His Thr Ser Thr Gly His Ser Gln Leu Pro Ala Ile
 65 70 75 80
 Pro Phe Asp Asn His Cys Gly Lys Arg Cys Arg Leu Gly Gly Lys Trp
 85 90 95
 Arg Ala Pro Leu Gln His Pro Gln Trp Lys
 100 105

<210> 317
 <211> 89
 <212> PRT
 <213> Homo sapiens

<400> 317
 Arg Arg Pro Thr Arg Pro Gln Glu Glu Gly Gly Ser Glu Ser Ser Thr
 1 5 10 15
 Met Thr Glu Leu Glu Thr Ala Met Gly Leu Ile Ile Asp Val Phe Ser
 20 25 30
 Arg Tyr Ser Gly Ser Glu Gly Ser Thr Gln Thr Leu Thr Lys Gly Glu
 35 40 45
 Leu Lys Val Leu Met Glu Lys Glu Leu Pro Gly Phe Leu Gln Leu Ser
 50 55 60
 Gly Pro Gly Leu Gly His Gln His Thr Leu Leu Leu Leu Phe Arg Ser
 65 70 75 80
 Ala Ser Trp Ser Arg Leu Val Pro Gln
 85

<210> 318
 <211> 151
 <212> PRT
 <213> Homo sapiens

<400> 318

```

Met Val Glu Gly Lys Glu Glu Gln Val Thr Ser Tyr Val Asp Val Gln
 1          5          10          15
Arg Ala Cys Ala Gly Ile Arg Gly Ala Phe Glu Lys Pro Gln Gly Ala
          20          25          30
Val Ala Arg Val His Ile Gly Gln Val Ile Met Ser Ile Cys Thr Lys
          35          40          45
Leu Gln Asn Lys Glu His Val Ile Glu Ala Leu Cys Lys Ala Asn Phe
          50          55          60
Lys Phe Pro Gly Arg Gln Asn Ile His Phe Ser Glu Lys Trp Asp Phe
          65          70          75          80
Thr Lys Phe Ser Val Asp Glu Phe Glu Asp Met Met Ala Glu Lys Gln
          85          90          95
Leu Ile Pro Asp Asn Cys Gly Val Lys Tyr Thr Pro Asn Arg Asp Pro
          100          105          110
Pro Asp Lys Arg Asp Gly Val Ala Leu Gln His Gly Leu Leu Leu Trp
          115          120          125
Gln Leu Leu Gln Asn Lys Ile Arg Leu His Gln Gly Arg Glu Lys Lys
          130          135          140
Pro Pro Lys Lys Ala Arg Arg
145          150

```

```

<210> 319
<211> 124
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(124)
<223> Xaa = X or * as defined in Table 6

```

```

<400> 319
Met Ser Arg Arg Lys Gln Gly Lys Pro Gln His Leu Ser Lys Arg Glu
 1          5          10          15
Phe Ser Pro Arg Asp Arg Glu Glu Val Thr Thr Cys Phe Pro Cys Pro
          20          25          30
Pro Pro Thr Pro Pro Gly Leu Val Thr Ser Pro Pro Ala Pro Arg Ala
          35          40          45
Arg Leu Gly Gln Pro Cys Ser Ala Arg Asn Glu Asn Leu Leu Glu Ala
          50          55          60
Asp Tyr Asp Pro Pro Glu Pro Ile Val Leu Arg Asn Thr Thr Ala Thr
          65          70          75          80
His Thr His Ser His Ser Val Ser Pro Ser Leu Tyr Asn Ser Asp Ser
          85          90          95
Pro Gln Pro Leu Lys His Leu Gly Ala Val Ser Ala Ala Glu Thr Gly
          100          105          110
Val Arg Gly Met Met Gly Met Tyr Leu Lys Pro Xaa
          115          120

```

```

<210> 320
<211> 1067
<212> PRT
<213> Homo sapiens

```

```

<400> 320
Met Cys Glu Leu Asp Ile Leu His Asp Ser Leu Tyr Gln Phe Cys Pro
 1          5          10          15
Glu Leu His Leu Lys Arg Leu Asn Ser Leu Thr Leu Ala Cys His Ala

```

			20					25				30			
Leu	Leu	Asp	Cys	Lys	Thr	Leu	Thr	Leu	Thr	Glu	Leu	Gly	Arg	Asn	Leu
		35					40					45			
Pro	Thr	Lys	Ala	Arg	Thr	Lys	His	Asn	Ile	Lys	Arg	Ile	Asp	Arg	Leu
	50					55					60				
Leu	Gly	Asn	Arg	His	Leu	His	Lys	Glu	Arg	Leu	Ala	Val	Tyr	Arg	Trp
	65			70					75					80	
His	Ala	Ser	Phe	Ile	Cys	Ser	Gly	Asn	Thr	Met	Pro	Ile	Val	Leu	Val
			85					90					95		
Asp	Trp	Ser	Asp	Ile	Arg	Glu	Gln	Lys	Arg	Leu	Met	Val	Leu	Arg	Ala
			100					105					110		
Ser	Val	Ala	Leu	His	Gly	Arg	Ser	Val	Thr	Leu	Tyr	Glu	Lys	Ala	Phe
		115					120					125			
Pro	Leu	Ser	Glu	Gln	Cys	Ser	Lys	Lys	Ala	His	Asp	Gln	Phe	Leu	Ala
	130					135					140				
Asp	Leu	Ala	Ser	Ile	Leu	Pro	Ser	Asn	Thr	Thr	Pro	Leu	Ile	Val	Ser
	145				150					155					160
Asp	Ala	Gly	Phe	Lys	Val	Pro	Trp	Tyr	Lys	Ser	Val	Glu	Lys	Leu	Gly
			165					170						175	
Trp	Tyr	Trp	Leu	Ser	Arg	Val	Arg	Gly	Lys	Val	Gln	Tyr	Ala	Asp	Leu
			180					185					190		
Gly	Ala	Glu	Asn	Trp	Lys	Pro	Ile	Ser	Asn	Leu	His	Asp	Met	Ser	Ser
		195				200						205			
Ser	His	Ser	Lys	Thr	Leu	Gly	Tyr	Lys	Arg	Leu	Thr	Lys	Ser	Asn	Pro
	210					215					220				
Ile	Ser	Cys	Gln	Ile	Leu	Leu	Tyr	Lys	Ser	Arg	Ser	Lys	Gly	Arg	Lys
	225				230					235					240
Asn	Gln	Arg	Ser	Thr	Arg	Thr	His	Cys	His	His	Pro	Ser	Pro	Lys	Ile
			245					250						255	
Tyr	Ser	Ala	Ser	Ala	Lys	Glu	Pro	Trp	Ile	Leu	Ala	Thr	Asn	Leu	Pro
			260					265					270		
Val	Glu	Ile	Arg	Thr	Pro	Lys	Gln	Leu	Val	Asn	Ile	Tyr	Ser	Lys	Arg
		275					280					285			
Met	Gln	Ile	Glu	Glu	Thr	Phe	Arg	Asp	Leu	Lys	Ser	Pro	Ala	Tyr	Gly
	290					295					300				
Leu	Gly	Leu	Arg	His	Ser	Arg	Thr	Ser	Ser	Ser	Glu	Arg	Phe	Asp	Ile
	305				310					315					320
Met	Leu	Leu	Ile	Ala	Leu	Met	Leu	Gln	Leu	Thr	Cys	Trp	Leu	Ala	Gly
			325						330					335	
Val	His	Ala	Gln	Lys	Gln	Gly	Trp	Asp	Lys	His	Phe	Gln	Ala	Asn	Thr
		340						345				350			
Val	Arg	Asn	Arg	Asn	Leu	Lys	Ile	Tyr	Ser	His	Met	Val	Thr	Leu	Trp
		355				360						365			
Gly	Asn	Tyr	Glu	Gly	Ile	Ser	Gln	Thr	Gln	Ala	Phe	Ala	Lys	Glu	Asn
	370				375						380				
Asn	Gln	Lys	Ala	Tyr	Lys	Glu	Thr	Tyr	Gly	Val	Ser	His	Ile	Thr	Arg
	385				390					395					400
His	Asp	Met	Leu	Gln	Ile	Pro	Lys	Gln	Gln	Gln	Asn	Glu	Lys	Tyr	Gln
			405					410					415		
Val	Pro	Gln	Phe	Asp	Gln	Ser	Thr	Ile	Lys	Asn	Ile	Glu	Ser	Ala	Lys
		420						425				430			
Gly	Leu	Asp	Val	Trp	Asp	Ser	Trp	Pro	Leu	Gln	Asn	Ala	Asp	Gly	Thr
		435				440						445			
Val	Ala	Glu	Tyr	Asn	Gly	Tyr	His	Val	Val	Phe	Ala	Leu	Ala	Gly	Ser
	450				455					460					
Pro	Lys	Asp	Ala	Asp	Asp	Thr	Ser	Ile	Tyr	Met	Phe	Tyr	Gln	Lys	Val
	465				470					475					480
Gly	Asp	Asn	Ser	Ile	Asp	Ser	Trp	Lys	Asn	Ala	Gly	Arg	Val	Phe	Lys
			485					490						495	
Asp	Ser	Asp	Lys	Phe	Asp	Ala	Asn	Asp	Pro	Ile	Leu	Lys	Asp	Gln	Thr
		500						505				510			
Gln	Glu	Trp	Ser	Gly	Ser	Ala	Thr	Phe	Thr	Ser	Asp	Gly	Lys	Ile	Arg
	515					520						525			
Leu	Phe	Tyr	Thr	Asp	Tyr	Ser	Gly	Lys	His	Tyr	Gly	Lys	Gln	Ser	Leu

	530					535					540					
Thr 545	Thr	Ala	Gln	Lys	Ala	Tyr	Arg	Leu	Glu	Ile	Val	Ser	Leu	Glu	Met	
Gln	Lys	Asn	Gly		Ala	Asp	Ala	Ala	Pro	Tyr	Arg	Gln	Ile	Glu	Tyr	
Trp	Ala	Leu	Gly	His	Gly	Asp	Asp	Ile	Lys	Lys	Ala	Val	Ala	Phe	Trp	
Ser	Ser	Gly	Trp	Pro	Val	Gly	Phe	Ser	Lys	Met	Glu	Lys	Ala	Gly	Lys	
Ile	Leu	Arg	Ser	Gln	Val	Lys	Phe	Pro	Glu	Tyr	Met	Glu	Glu	Ser	Ser	
Cys 625	Leu	Gly	Arg	Gly	Ser	Leu	Met	Ser	Leu	Asn	Asn	Thr	Ser	Ser	Ser	
Asn	Gly	Ser	Phe	Ile	Phe	Val	Leu	Pro	Leu	Lys	Leu	Leu	Arg	Val	Gly	
Asp	Thr	Tyr	Asn	Ser	Ser	Asp	Gln	Ser	Arg	Met	Ala	Trp	Arg	Leu	Thr	
Ile	Glu	Phe	Gly	Gly	Ser	Glu	Leu	His	Leu	Gly	Val	Arg	Glu	Glu	Ala	
Gly	His	Gln	Lys	Gly	Leu	Val	His	Glu	Ser	Gly	Asn	Pro	Ala	Arg	Ser	
Ser 705	Gly	Ser	Asp	Pro	Gln	His	Ala	Arg	His	Arg	Gln	Pro	Ser	Ala	Thr	
Arg	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Leu	Pro	Ala	Pro	
Leu	Ser	Leu	Pro	Val	Pro	Thr	Ser	Ala	Ile	Gln	Val	Arg	Val	Thr	Ala	
Tyr	Pro	Leu	Leu	Ala	Gln	Cys	Leu	Gln	Ala	Ala	Phe	Pro	Pro	Leu	Leu	
Gly	Ser	Gly	Cys	Gly	Gln	Glu	Gly	Thr	Gly	Ala	Gly	Gly	Gly	Gly	Gly	
Ala 785	Ala	Gly	Val	Arg	Glu	Gln	Leu	Glu	Asp	Arg	Arg	Ala	Ala	Ala	Glu	
Pro	Gly	Asp	Leu	Pro	Gly	Gly	Lys	Arg	Val	Arg	Gly	Arg	Gly	Ala	Arg	
Glu	Gly	Pro	Gly	Val	Gly	Ala	Glu	Gly	Pro	Pro	Leu	Glu	Arg	Asn	Arg	
Pro	Ser	Ser	Pro	Leu	Pro	Trp	Leu	Ala	Ala	Pro	Ala	Ala	Gly	Ala	Ser	
Gln	Phe	Ala	Glu	Ile	Gln	Gly	Ala	Gly	Lys	Gly	Glu	Met	Arg	Ala	Lys	
Asp 865	Ala	Glu	Arg	Gly	Arg	Ala	Lys	Leu	Arg	Gly	Glu	Leu	Ser	Ser	Ser	
Gly	Arg	Lys	Ile	Phe	Asp	Pro	Asp	Asp	Leu	Tyr	Ser	Gly	Val	Asn	Phe	
Ser	Lys	Val	Leu	Ser	Thr	Leu	Leu	Ala	Val	Asn	Lys	Ala	Thr	Glu	Asp	
Gln	Leu	Ser	Glu	Arg	Pro	Cys	Gly	Arg	Ser	Ser	Ser	Leu	Ser	Ala	Ala	
Asn	Thr	Ser	Gln	Thr	Asn	Pro	Gln	Gly	Ala	Val	Ser	Ser	Thr	Val	Ser	
Gly 945	Leu	Gln	Arg	Gln	Ser	Lys	Thr	Val	Glu	Met	Thr	Glu	Asn	Gly	Ser	
His	Gln	Leu	Ile	Val	Lys	Ala	Arg	Phe	Asn	Phe	Lys	Gln	Thr	Asn	Glu	
Asp	Glu	Leu	Ser	Val	Cys	Lys	Gly	Asp	Ile	Ile	Tyr	Val	Thr	Arg	Val	
Glu	Glu	Gly	Gly	Trp	Trp	Glu	Gly	Thr	Leu	Asn	Gly	Arg	Thr	Gly	Trp	
Phe	Pro	Ser	Asn	Tyr	Val	Arg	Glu	Ile	Lys	Ser	Ser	Glu	Arg	Pro	Leu	
Ser	Pro	Lys	Ala	Val	Lys	Gly	Phe	Glu	Thr	Ala	Pro	Leu	Thr	Lys	Asn	
Tyr	Tyr	Thr	Val	Met	Ser	Arg	Ser	Leu	Thr	Ser	Thr	Val	Leu	Lys	Asn	

1045 1050 1055
 Ser Lys Val Ala Arg Ile His Ser Lys Pro Tyr
 1060 1065

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<210> 321
<211> 191
<212> PRT
<213> Homo sapiens
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<400> 321																
Arg 1	Ser	Pro	Thr	Leu 5	Ser	Ser	Pro	Pro	Pro	Ala	Ser	Lys	Ala	Gln	Ala	
Leu	Ala	Leu	Arg	Ser	Glu	Ala	Gln	Ala	Gln	Met	Pro	Arg	Leu	Pro	Ala	
			20					25					30			
Pro	Arg	Val	Arg	Arg	Ser	Ser	Ala	Ala	Ala	Ser	Ala	Ala	Ala	Arg	Ser	
		35					40					45				
Leu	Ala	Glu	Thr	Phe	Ser	Gly	Lys	Glu	Cys	Gln	Trp	Thr	Asp	Ala	Cys	
		50				55					60					
Leu	Ser	His	Pro	Cys	Ala	Asn	Gly	Ser	Thr	Cys	Thr	Thr	Val	Ala	Asn	
65					70					75					80	
Gln	Phe	Ser	Cys	Lys	Cys	Leu	Thr	Gly	Phe	Thr	Gly	Gln	Lys	Cys	Glu	
				85					90					95		
Thr	Asp	Val	Asn	Glu	Cys	Asp	Ile	Pro	Gly	His	Cys	Gln	His	Gly	Gly	
			100					105					110			
Thr	Cys	Leu	Asn	Leu	Pro	Gly	Ser	Tyr	Gln	Cys	Gln	Cys	Leu	Gln	Gly	
		115				120					125					
Phe	Thr	Gly	Gln	Tyr	Cys	Asp	Ser	Leu	Tyr	Val	Pro	Cys	Ala	Pro	Ser	
	130					135				140						
Pro	Cys	Val	Asn	Gly	Gly	Thr	Cys	Arg	Gln	Thr	Gly	Asp	Phe	Thr	Phe	
145					150					155					160	
Glu	Cys	Asn	Cys	Leu	Pro	Glu	Thr	Val	Arg	Arg	Gly	Thr	Glu	Leu	Trp	
				165					170					175		
Glu	Arg	Asp	Arg	Glu	Val	Trp	Asn	Gly	Lys	Glu	Pro	Asp	Glu	Asn		
			180					185					190			

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<210> 322
<211> 71
<212> PRT
<213> Homo sapiens
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[illegible]

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<210> 323
<211> 72
<212> PRT
<213> Homo sapiens
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<400> 323

Glu Ser Gln Ser Leu Glu Thr Gly Leu Arg Ala Leu Ile Trp Ser Thr
 1 5 10 15
 Arg Lys Pro Gly Gly Pro Val Leu Gly Gly Leu Val Leu Ile Lys Trp
 20 25 30
 Ala Trp Ala Ser Arg Ser Pro Ala Ser Pro Ser Asp Pro Ser Pro Gly
 35 40 45
 Pro Asn Leu Cys Cys Ser Pro Thr Ser Pro Ala Thr Lys Pro Arg Val
 50 55 60
 Asp Gly Pro Phe Val Ile Arg Asn
 65 70

<210> 324

<211> 205

<212> PRT

<213> Homo sapiens

<400> 324

Met Asn Trp Val Leu Gln Lys Phe Ile Thr Ala Trp Lys Phe Met Gly
 1 5 10 15
 Tyr Arg Lys Ser Ser Asn Ser Ala Arg Gly Ser Thr Ile Lys Glu His
 20 25 30
 Ile Glu Leu Asp Ala Gln Arg Pro Val Arg Arg Ser Gly Pro Ile Gln
 35 40 45
 Ala Ser Gly Ala His Pro Lys Lys Gly Arg Gly Val Ser Cys Ser Val
 50 55 60
 Glu Glu Pro Ser Asp Gln Gln Ser Pro Ser Pro Pro Ser Pro Leu Thr
 65 70 75 80
 Phe Gln Pro Lys Asp Gly Glu Ile Asn Phe Ser Val Ile Gly Gln Tyr
 85 90 95
 Val Asp Tyr Leu Val Lys Glu Gln Gly Val Lys Asn Ile Phe Gly Lys
 100 105 110
 Ser Thr Leu Gly Met Ser Leu His Val Ser Ser Ser Val Phe Arg Arg
 115 120 125
 Tyr Ile Leu Pro Gly Tyr Gln Pro Arg Gly His Thr Val Met Val Ser
 130 135 140
 Gln Val Asn Ile Asp Phe Gln Thr Arg Glu Ala Thr Arg Lys Asn Leu
 145 150 155 160
 Gln Glu Pro Ser Leu Thr Cys Phe Asp Gln Ala Gln Gly Lys Val His
 165 170 175
 Ser Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Arg Ser Lys Met
 180 185 190
 Tyr Leu Asp Leu Leu Ser Gln Ser Gln Arg Arg Leu Ser
 195 200 205

<210> 325

<211> 222

<212> PRT

<213> Homo sapiens

<400> 325

Met Val Met Ser Phe Val Lys Pro Gly Val Lys Glu Lys Glu Gln Val
 1 5 10 15
 Lys Lys Arg Asp Gly Glu Phe Asn Ser Glu His Ala Glu Leu Asp Val
 20 25 30
 Pro Ala Arg Asp Thr Lys Arg Lys Phe Trp Glu Pro Thr Arg Leu Ser

		35						40						45					
Ser	Thr	Leu	Arg	Thr	Ser	Ser	Asp	Pro	Leu	Phe	Ser	Val	Pro	Ile	Ser				
	50					55					60								
Ile	Thr	Met	Val	Cys	Glu	Pro	Gly	Ser	Lys	Ser	Leu	Gln	Ser	Cys	Cys				
65					70					75					80				
Leu	Thr	Ala	Gly	Gly	Ala	Asn	Val	Trp	Glu	Lys	Ser	Thr	Cys	Arg	Lys				
				85					90					95					
Lys	Ser	Arg	Gln	Leu	Val	Leu	Arg	Asn	Val	Lys	Val	Pro	Gly	Lys	Ser				
			100					105					110						
Pro	Cys	Gly	Glu	Leu	Leu	Pro	Ile	Leu	Lys	Lys	Asn	Gln	Leu	Asn	Ile				
			115				120					125							
Leu	Leu	Leu	Gln	Pro	Val	Asp	Thr	Glu	Thr	Leu	Glu	Gly	Pro	Pro	Gly				
						135					140								
Leu	Gly	Leu	Asp	Ala	Glu	Gly	Pro	Glu	Lys	Arg	His	Ser	Trp	Ile	Leu				
145					150					155					160				
Leu	Pro	Cys	Pro	Gly	Ile	Asp	His	Thr	Ser	Gly	Leu	Glu	Val	Met	Ser				
				165					170					175					
Asp	Leu	Tyr	His	Arg	Lys	Gly	Asn	Ser	Leu	His	Pro	Gln	Gly	Lys	Arg				
			180				185						190						
Thr	Lys	Asp	Ala	Arg	Lys	Glu	Ser	Phe	Pro	Gln	Lys	Met	Gly	Gln	Phe				
			195				200					205							
Pro	Leu	Gln	Ser	Leu	Ala	Val	Ile	Tyr	Pro	Glu	Ala	Gly	Thr						
						215					220								

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<210> 326
<211> 680
<212> PRT
<213> Homo sapiens
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<400> 326															
Met 1	Glu	Glu	His	Ser 5	Met	Leu	Met	Gly	Arg 10	Lys	Asn	Gln	Tyr	Arg 15	Glu
Asn	Gly	Arg	Ile 20	Ala	Gln	Glu	Leu	Glu	Lys 25	Thr	Thr	Leu	Lys 30	Phe	Ile
Trp	Asn	Gln	Lys 35	Arg	Ala	Cys	Ile 40	Thr	Lys	Ser	Asn	Leu	Ser 45	Gln	Lys
Asn	Lys 50	Ala	Gly	Gly	Ile	Thr 55	Leu	Pro	Asp	Phe	Lys 60	Leu	Tyr	Tyr	Lys
Ala 65	Thr	Val	Thr	Lys 70	Thr	Ala	Trp	Tyr	Trp	Tyr 75	Gln	Asn	Arg	Asp 80	Ile
Asp	Gln	Trp	Asn 85	Arg	Thr	Glu	Pro	Ser	Glu 90	Ile	Met	Pro	His 95	Ile	Tyr
Asn	Tyr	Leu	Ile 100	Phe	Asp	Lys	Pro	Glu	Lys 105	Asn	Lys	Gln	Trp 110	Gly	Lys
Asp	Ser 115	Leu	Phe	Asn	Lys	Arg	Phe 120	Trp	Glu	Asn	Trp	Leu	Ala 125	Ile	Phe
Arg 130	Lys	Leu	Lys	Leu	Asp 135	Pro	Phe	Leu	Thr	Pro 140	Tyr	Thr	Lys	Ile	Asn
Ser 145	Arg	Trp	Ile	Lys 150	Asp	Leu	His	Val	Arg 155	Pro	Lys	Thr	Ile	Lys 160	Thr
Leu	Glu	Glu	Asn 165	Pro	Gly	Ile	Thr	Ile	Gln 170	Asp	Thr	Gly	Met 175	Gly	Lys
Asp	Phe 180	Thr	Ser	Lys	Thr	Pro	Lys 185	Ala	Met	Ala 190	Thr	Lys	Ala 195	Lys	Ile
Asp	Lys 195	Trp	Asp	Leu	Ile	Lys	Leu 200	Lys	Ser	Phe 205	Cys	Thr	Ala 210	Lys	Glu
Thr 210	Thr	Ile	Arg	Val	Asn 215	Arg	Gln	Pro	Thr	Lys 220	Trp	Glu	Lys	Ile	Phe
Ala 225	Thr	Tyr	Ser	Ser 230	Asp	Lys	Gly	Leu	Thr 235	Ser	Arg	Ile	Tyr	Asn 240	Glu
Leu	Lys	Gln	Ile	His	Lys	Lys	Lys	Thr	Asn	Asn	Pro	Ile	Arg	Lys	Trp

					245					250				255	
Ala	Lys	Asp	Met	Asn	Arg	His	Phe	Ser	Lys	Glu	Asp	Ile	Tyr	Ala	Ala
			260					265					270		
Lys	Lys	His	Met	Lys	Lys	Cys	Ser	Pro	Ser	Leu	Ala	Ile	Arg	Glu	Met
			275				280						285		
Gln	Ile	Lys	Thr	Thr	Met	Arg	Tyr	His	Leu	Thr	Ser	Val	Arg	Met	Ala
			290			295					300				
Ile	Ile	Gln	Lys	Ser	Gly	Asn	Asn	Arg	Val	Leu	Pro	Leu	Ala	Pro	Leu
305					310					315					320
Ala	Leu	Ala	Ala	Leu	Trp	Met	Asp	Pro	Val	Met	Pro	Gly	Met	Asp	Gly
				325					330					335	
Leu	Leu	Gly	Asp	Ser	Glu	Ser	Phe	Gln	Gly	Leu	Ser	Ala	Thr	Phe	Phe
			340				345						350		
Ala	Ser	Val	Phe	His	Ser	Ala	Leu	His	Ile	Asp	Ser	Ala	Pro	Gly	Pro
			355			360						365			
Cys	Ile	Gly	Pro	Gly	Asp	Ser	Ser	Ala	Asp	Ser	Ser	Pro	Thr	Phe	Leu
			370			375					380				
Pro	Pro	Glu	Ala	Lys	Arg	Lys	Asn	Tyr	Leu	Leu	Leu	Trp	Arg	Lys	Asn
385					390					395					400
Leu	Lys	Lys	Phe	Ser	Asp	Asp	Pro	Lys	Arg	Leu	Ile	Glu	Gly	Phe	Pro
				405					410					415	
Lys	Leu	Ala	Leu	Thr	Phe	Arg	Leu	Ile	Trp	Lys	Asp	Ile	Asn	Val	Leu
			420				425						430		
Leu	Gly	Gln	Ala	Leu	Leu	Gln	Glu	Arg	Gln	Thr	Ile	Cys	Gly	Ala	
			435			440							445		
Ala	Ile	His	Cys	Arg	Asn	Asp	Leu	His	Leu	Glu	Asn	Ala	Asn	Tyr	Pro
					455						460				
Gly	Gly	Ala	Thr	Ala	Val	Pro	Gln	Leu	Asp	Pro	Asn	Gln	Asp	Tyr	Asn
465					470					475					480
Ala	Lys	Ala	Gly	Ile	Trp	Ala	Arg	Asn	His	Arg	Leu	Leu	Cys	Leu	Ile
				485				490						495	
Glu	Thr	Thr	Thr	Gln	Gln	Pro	Thr	Asn	Ala	His	Ser	Pro	Gln	Thr	Gln
				500				505					510		
Arg	Gln	Gln	His	Asp	Thr	Asp	Lys	Pro	Gln	Pro	Asn	Pro	Pro	Ala	Lys
			515			520						525			
Thr	Thr	Gly	Val	Pro	Val	Ser	Phe	Leu	Ala	Phe	Leu	Tyr	Gln	Tyr	Leu
						535					540				
Cys	Gly	His	Ile	Ser	Ile	Ser	Trp	Pro	Val	Val	Ile	Leu	Lys	Tyr	Ala
545					550					555					560
Ala	Ser	Val	Tyr	Gly	Ile	Ser	Leu	Ala	Asp	Arg	Lys	Arg	Gln	Tyr	Asp
				565					570					575	
Arg	Tyr	Phe	Arg	Tyr	Glu	Arg	Leu	Arg	Thr	Ile	Lys	Pro	Asn	Phe	Leu
			580					585					590		
Pro	Phe	Gln	Ile	Phe	Lys	Ser	Gly	Ser	Val	Val	Lys	Leu	Lys	Ala	Gly

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<210> 327
<211> 371
<212> PRT
<213> Homo sapiens
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<400> 327

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Met Leu Met Val Tyr Pro Arg Thr Asn Lys Gln Asn Gln Lys Lys Lys
 1      5      10      15
Trp Lys Val Glu Pro Pro Thr Pro Gln Glu Pro Gly Pro Ala Lys Val
      20      25      30
Ala Val Thr Thr Ser Ser Ser Ser Ser Ser Ile Pro Ser Ala Glu
      35      40      45
Lys Val Pro Thr Thr Lys Ser Thr Leu Trp Gln Glu Glu Met Arg Thr
      50      55      60
Lys Asp Gln Pro Asp Gly Ser Ser Leu Ser Pro Ala Gln Ser Pro Ser
      65      70      75      80
Gln Ser Gln Pro Pro Ala Ala Ser Ser Leu Arg Glu Pro Gly Leu Glu
      85      90      95
Ser Lys Glu Glu Glu Ser Ala Met Ser Ser Asp Arg Met Asp Cys Gly
      100      105      110
Arg Ile Pro Ser Thr Pro Asn His Arg Arg Ser Gln Val Ile Glu Lys
      115      120      125
Phe Glu Ala Leu Asp Ile Glu Lys Ala Glu His Met Glu Thr Asn Ala
      130      135      140
Val Gly Pro Ser Pro Ser Ser Asp Thr Arg Gln Gly Arg Ser Glu Lys
      145      150      155      160
Arg Ala Phe Pro Ser Lys Gln Asp Phe Thr Asn Glu Ala Pro Pro Gln
      165      170      175
Ala Pro Leu Pro Asp Ala Ser Ala Ser Pro Val Ser Thr Pro Lys Ser
      180      185      190
Gln Val Thr Gly Gln Glu Gly Gln Asn Ile Ser Trp Asp Met Ala Val
      195      200      205
Val Leu Lys Ala Thr Gln Glu Ala Pro Ala Ala Ser Thr Leu Gly Ser
      210      215      220
Tyr Ser Leu Pro Gly Thr Leu Ala Lys Ser Glu Ile Leu Glu Thr His
      225      230      235      240
Gly Thr Met Asn Phe Leu Asp Ser Ser Pro Gln Val Arg Tyr His Pro
      245      250      255
Arg Asn Leu Gly Thr Ala Cys Asn Gln Ala Gly Leu Asp Arg Tyr Tyr
      260      265      270
Pro Glu Gly Pro Leu Pro Arg Ser Gly Asp Asp Thr Val Leu Ser Pro
      275      280      285
Arg Pro Ala Trp Ser Lys Leu Ala Ala Thr Arg Ser Gln Arg Leu Asp
      290      295      300
Pro Arg Gln Arg Gly Ser Thr Glu Arg Glu Lys Gly Glu Ala His Asn
      305      310      315      320
Asp Pro Leu Ala Ala Pro Ile Ser Ala Ala Gly Ser Arg Arg Gly
      325      330      335
Ala Leu Ala Ser Trp Leu Ala Ser Pro Thr Arg Ser Gln Asn Pro Ala
      340      345      350
Arg Pro Pro Thr Pro Asp Cys Arg Ala Pro Leu Thr Glu Ser Ala Arg
      355      360      365
Pro Thr Ser
      370

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<210> 328

<211> 117

<212> PRT

<213> Homo sapiens

<400> 328

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Met Gly Lys Trp Asp Gly Gly Phe Asn Phe Met Val Phe Cys Val Leu
 1      5      10      15
Glu Asn Thr Cys Ser Leu Asn Arg Ser Leu Leu Glu Asn Leu Ile Phe
      20      25      30
Ala Thr Leu Lys Ile Ser Trp Gly Gly Ala Gly Ile Lys Gly Trp Asn

```

```

      35      40      45
His Met Lys Ala Gln Leu Leu Thr Cys Val Val Phe Asp Ala Gly Phe
      50      55      60
Gln Leu Ser Pro Gln Gly Ser Leu Glu Gln Lys His Leu Ile Leu Tyr
      65      70      75      80
Pro Glu Leu Thr Gly Pro Ile Glu Leu Asp Pro Ile Cys Tyr His His
      85      90      95
His Leu Ser Asn Leu Leu Ser Gln Thr Pro Lys Ala Ser Phe Glu Val
      100      105      110
Leu His Gln Asn His
      115

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<210> 329
<211> 256
<212> PRT
<213> Homo sapiens

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      <400> 329
Pro Ile Trp Ala Thr Arg Cys Tyr Gly Gly Trp Arg Gly Ser Leu Phe
      1      5      10      15
Leu Glu Leu Pro Arg Cys Asp Gly Pro Leu Ser Arg Trp Gly Trp Ala
      20      25      30
Ala Pro Lys Met Ala Ala Ser Leu Leu Phe Ser Asp Gln Gly Phe Leu
      35      40      45
Ala Ser Trp Ile Pro Arg Asn Gly Thr Leu Gly His Ala Met Ser Gly
      50      55      60
Ile Ala Leu Leu Glu Ala Val Gly His Gly Arg Glu Leu Trp Asn Pro
      65      70      75      80
Ala Thr Ser Ala Ala Ser Val Ile Ser Asn Thr Ser Ser Asp Ala Asn
      85      90      95
Gln Phe Pro Lys Leu Pro Leu Gly Glu Ile Ser Pro Asp Lys Glu Lys
      100      105      110
Ser Tyr Trp Ser Ser Asn Pro Thr Lys Asn Asn Pro Lys Glu Thr Thr
      115      120      125
Arg Val Ala Val Phe Ala Arg Ile Leu Asp Val Asn Asp Asn Ala Pro
      130      135      140
His Phe Ala Val Phe Tyr Asp Thr Phe Val Cys Glu Asn Ala Arg Pro
      145      150      155      160
Gly Gln Arg Asp Ala Cys Gly Arg Leu Gly Asp Trp Asp Ser Glu Lys
      165      170      175
Gln Glu Gly Arg Lys Gly Phe Thr Ser Thr Asn Ser Val Ile Leu His
      180      185      190
Lys Lys Arg Thr Lys Arg Ser Val Leu Gly Gly Asp Lys Phe Trp Gln
      195      200      205
Lys Lys Ser Pro Glu Ser Pro Gln Gly Asp Phe Gln Asp Ser Arg Ser
      210      215      220
Leu Arg Ser Thr Val Lys Phe His Lys Ser Thr Arg Lys Leu Gln Gly
      225      230      235      240
Glu Val Glu Lys Ser Ser Val Ala Arg Asn Tyr Gly Phe Asp Pro Leu
      245      250      255

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<210> 330
<211> 96
<212> PRT
<213> Homo sapiens

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<220>

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<221> misc_feature
 <222> (1)...(96)
 <223> Xaa = X or * as defined in Table 6

<400> 330
 Gly Cys Leu Glu His Glu Ala Ser Ser Ala Tyr Glu Trp Leu Trp Ser
 1 5 10 15
 Leu Cys Ala Leu Leu Asp Met Tyr Thr Ala Gly Pro Thr Lys Thr Gln
 20 25 30
 Thr Leu Gln Pro Met Gly Gln Pro Asn Leu Lys Gly Asp Gly Gly Phe
 35 40 45
 Thr Arg Glu Ser Thr Gly Phe Met Gln Leu Pro Ala Asp Phe Ile Ser
 50 55 60
 Ser Leu Ile Cys His Glu Thr Trp Val Pro Gly Lys Pro Ser Thr Ala
 65 70 75 80
 Met His Arg Gly Arg Tyr Trp Ala Glu Pro Ile Met Leu Pro Lys Xaa
 85 90 95

<210> 331
 <211> 142
 <212> PRT
 <213> Homo sapiens

<400> 331
 Met Ser Glu Lys Asn Thr Pro Leu Val Leu Ser Gly Glu Asn Gln Lys
 1 5 10 15
 Lys Gly Arg Glu Ile Gly Val Cys Arg Lys Gln Ser Gln Cys Asp His
 20 25 30
 Gln Asp Asn Asn Ser His Thr Leu Arg Phe Ser Ser Tyr Ser Ser Ser
 35 40 45
 Ser Gly Pro Val Thr Leu Val Ser Phe His Ser His Asn Tyr Pro Ser
 50 55 60
 Lys Val Leu Leu Gln Gly Asn Leu Asp Thr Glu Thr Cys Thr Glu Arg
 65 70 75 80
 Arg Gln Arg Glu Ile Trp Thr Gln Arg His Glu Gly Lys Cys Gly His
 85 90 95
 Arg Asp Met Tyr Arg Glu Lys Thr Lys Arg Lys Tyr Arg Glu Lys Ala
 100 105 110
 Ile Tyr Lys Leu Arg Lys Gly Pro Glu Thr Asp Pro Ser Ser Gln Pro
 115 120 125
 Ser Glu Arg Thr Asn Pro Ala Asn Thr Leu Ile Ser Asp Ser
 130 135 140

<210> 332
 <211> 424
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(424)
 <223> Xaa = X or * as defined in Table 6

<400> 332
 Thr Ile Ser Trp Arg Gln Gly Arg Gly Gly Glu Ala Gly Arg Arg Leu

1	5	10	15
Trp His Thr	Pro Pro Gln Val Lys His Leu Glu Pro Gly His Pro Glu		
	20	25	30
Gln Gln Ala Arg	Lys Ala Gln Ile Gln Gly Gln Pro Pro Ala Pro Gly		
	35	40	45
Trp Asp Leu Thr	Gln Gly Glu Gln Ala Gly Asn Ile His Gln His Cys		
	50	55	60
Gly Gln Ser Arg	Gly Xaa Gln Gln His Gln Lys Asp Pro Xaa Gly His		
	65	70	75
Arg Phe Ala Glu	Gly Met Gln Ser Leu Ser Lys Glu Leu Gln Ser Asp		
	85	90	95
Xaa Thr Ser Arg	Lys Gly Gly Phe Arg Val Pro Cys Ser His Asn Arg		
	100	105	110
Glu Pro Pro Thr	Arg Pro Gly Asp Pro Cys Asp Ser Pro Ala Gly Leu		
	115	120	125
Gly Leu Gln Glu	Cys Arg Ala Arg Tyr Arg Pro Gly Lys Pro Ser Ser		
	130	135	140
Pro Pro Arg Gly	Gln Ser Arg Ala Thr Gly Pro Val Arg Trp His Pro		
	145	150	155
Ser Pro Ser Arg	Asn Xaa Gly Pro Pro Gly Ser Arg Pro Ala Pro Gly		
	165	170	175
Thr Asp Pro Ala	Pro Gly Arg Pro Pro Gly Arg Pro Leu Ala Ala Ser		
	180	185	190
Gly Leu Leu Pro	Asn Ser Pro Pro Ala Pro Gly Ser Pro Gln Gly Pro		
	195	200	205
Pro Pro Pro Arg	Gly Ser Asn Arg Pro Arg Phe Pro His Trp Leu Arg		
	210	215	220
Arg Pro Ala Gly	Arg Gly Ala Pro Cys Xaa Pro Gln Pro Arg Ser Pro		
	225	230	235
Gln Gln His Ile	Pro Glu His Arg Thr Lys Pro Val Pro Ala Pro Glu		
	245	250	255
Pro Pro Ser Gly	Ser Arg Asn Thr Asp Pro Pro Gly Gln Pro Arg Ala		
	260	265	270
Arg Gly Thr Trp	Lys Ala Ser Pro Gly His Arg Ala Asp Ser Ala Ser		
	275	280	285
Arg Arg Ala Ser	Phe Leu Phe Arg Cys Leu Ala Asn Leu Gln Arg Ser		
	290	295	300
Leu Lys Gln Met	Arg Gly Lys Leu His Ser Gln Lys Ala Gln Phe Trp		
	305	310	315
Phe Ile Leu Asn	Gly Phe Ile Gly Gly Val Ile Gly Arg Arg Met Thr		
	325	330	335
Asp Cys Gln Ala	Cys Glu Pro Arg Leu Arg Ser Ile Gln Cys Gln Leu		
	340	345	350
Pro Glu Ser Tyr	Thr Ser Leu Cys His Pro Ala Ala Leu Thr Gln Ser		
	355	360	365
Gly Pro Lys Asn	Val Leu Glu Arg Asp Gln Pro Ser Ala Cys Ser Leu		
	370	375	380
Lys Thr Pro Ala	Gln Thr Cys Leu Pro Gln Cys Ser Leu His Trp Thr		
	385	390	395
Leu Arg Asp Asp	Gln Thr Gln Pro Leu Thr Ala Pro Ser Ser Thr Met		
	405	410	415
Asn Gly Ala Tyr	Arg Met Lys Cys		
	420		

<210> 333

<211> 49

<212> PRT

<213> Homo sapiens

<400> 333

Pro Leu Val Val Cys Leu Leu Glu Phe Tyr Cys Thr His Leu Arg Asp

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      1           5           10           15
Gly Leu Asn Ser Val Gln Leu Ala Tyr Arg Gly Cys Arg Pro Thr Glu
      20           25           30
Ala Thr Phe Thr Pro Ala Arg Arg Pro Trp Gln Ala Arg Ala Pro Cys
      35           40           45
Arg

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```

<210> 334
<211> 30
<212> PRT
<213> Homo sapiens

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      <400> 334
Met Ala Glu Tyr Asp Leu Thr Thr Arg Ile Ala His Phe Leu Asp Arg
      1           5           10           15
His Leu Val Phe Pro Leu Leu Glu Phe Leu Ser Val Lys Glu
      20           25           30

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<210> 335
<211> 123
<212> PRT
<213> Homo sapiens

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      <400> 335
Arg Gly Ala Arg Ile Arg Tyr Ala Val Cys Val Cys Val Cys Val Cys
      1           5           10           15
Val Tyr Pro Cys Val His Val Cys Thr Cys Val Arg Met Cys Leu Cys
      20           25           30
Val Cys Val Cys Val Cys Val Cys Val Cys Val Cys Gly Gly Cys Lys
      35           40           45
Cys Thr Cys Gly Pro Thr Glu Gly Gly Glu Lys Ala Trp Leu Phe Thr
      50           55           60
Ser Ile Gln Glu Gly Arg Arg Cys Gly Trp Ser Ser Ser Leu Arg Gly
      65           70           75           80
Ser Ala Ala Gly Arg Asp Leu Tyr Ser Ala Arg Leu Phe Ala His Arg
      85           90           95
Leu Leu Leu Leu Glu Gly Arg Pro Trp Gln Asp Ala Gly Ala Pro Ser
      100          105          110
Ala Ala Arg Ile Ser Arg Ser Glu Pro Trp Ser
      115          120

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10472

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; C12N 1/20, 5/02, 15/00, 15/12; C12P 21/06; C12Q 1/68

US CL : 435/6, 69.1, 252.33, 320.1, 325; 536/23.1, 23.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 69.1, 252.33, 320.1, 325; 536/23.1, 23.5

Documentation searched other than *minimum documentation* to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database GenBank, Accession No. L29164, 16 May 1995 (16.06.95), see entire entry.	2, 19
---		-----
A		1, 3-9

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

03 August 2001 (03.08.2001)

Date of mailing of the international search report

30 AUG 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

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Authorized officer

Marianne P. Allen

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10472

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 and 19 with respect to SEQ ID NO: 1

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10472

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-9 and 19 drawn to polynucleotides.

Group II, claims 10-11 and 20, drawn to polypeptides.

Group III, claim 12, drawn to antibodies.

Group IV, claims 13-15, drawn to methods of detection using polynucleotides.

Group V, claim 16, drawn to methods of detection using polypeptides.

Group VI, claims 17-18, drawn to methods of identifying compounds that bind to a polypeptide.

Group VII, claim 21, drawn to a polypeptide array.

Group VIII, claims 22-26, drawn to a polynucleotide array.

Group IX, claim 27, drawn to a method of treatment using a polypeptide.

Group X, claim 28, drawn to a method of treatment using an antibody.

Group XI, claim 29, drawn to a method of detecting bone marrow cells by means of polynucleotides.

Group XII, claim 30, drawn to a method of detecting bone marrow cells by means of polypeptides.

The inventions listed as Groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

For each of the above named groups, each SEQ ID NO. recited in the claims is considered to be a different inventive concept. If no additional fees are paid and in the absence of a request to search a specific sequence, Group I will be examined with respect to SEQ ID NO: 1. Each SEQ ID NO. has a different structure and does not share an obvious special technical feature with any other SEQ ID NO. With respect to Groups VI and VIII, each different subset of polypeptides or polynucleotides on the array is considered to be a different inventive concept. The inventions listed as Groups I-XII do not relate to a single inventive concept because the compositions of Groups I, II, III, VII, and VIII differ structurally and functionally and do not share any obvious special technical feature. The methods of Groups IV, V, IX, X, XI, and XII each have different starting materials, method steps, and/or goals. For purposes of calculating the number of inventions, each group embraces at least 168 SEQ ID NOS. (directly or by dependency), and as such, 12 groups multiplied by 168 SEQ ID NOS. gives 2016 inventions.